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Title page:

Safety and tolerability of natural and synthetic cannabinoids in adults aged over 50 years: a systematic review and meta-analysis

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ABSTRACT

Background: Cannabinoid-based medicines (CBMs) are being used widely in the elderly. However, their safety and tolerability in older adults remains unclear. We aimed to conduct a systematic review and meta- analysis of safety and tolerability of cannabinoid-based medicines (CBMs) in adults of age ≥50 years.

Methods and findings:

A systematic search was performed using MEDLINE, PubMed, EMBASE, CINAHL PsychInfo, Cochrane Library and ClinicalTrials.gov (1st Jan 1990 to 31st Oct 2020). Randomised clinical trials (RCTs) of CBMs in those with mean age of ≥50 years for all indications, evaluating the safety/tolerability of CBMs where adverse events have been quantified were included. Study quality was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed. Two reviewers conducted all review stages independently. Where possible, data were pooled using random-effects meta-analysis. Effect sizes were calculated as incident rate ratio (IRR) for outcome data such as AEs, SAEs and death and risk ratio (RR) for withdrawal from study and reported separately for studies using THC, THC:CBD combination and CBD. 46 RCTs were identified as suitable for inclusion of which 31 (67%) were conducted in the UK and Europe. There were 6216 patients (mean age 58.6± 7.5 years; 51% male) included in the analysis, with 3469 receiving CBMs. Compared with controls, delta-9-tetrahydrocannabinol (THC)-containing CBMs significantly increased the incidence of all-cause and treatment-related Adverse Events (AEs): THC alone (IRR:1.42 [95% CI,1.12 -1.78]) and (IRR: 1.60 [95% CI, 1.26 -2.04]); THC: cannabidiol (CBD) combination (IRR:1.58 [95% CI,1.26 -1.98]) and (IRR:1.70 [95% CI,1.24 -2.33]) respectively. IRRs of Serious AEs (SAEs) and deaths were not significantly greater under CBMs containing THC with or without CBD. THC:CBD combination (RR:1.40 [95% CI,1.08 -1.80]) but not THC alone (RR:1.18 [95% CI,0.89 -1.57]) significantly increased risk of AE-related

withdrawals. CBD alone did not increase the incidence of all-cause AEs (IRR: 1.02 [95% CI,0.90 -1.16]) or other outcomes as per qualitative synthesis. AE-related withdrawals were significantly associated with THC dose in THC only [QM (df= 1)= 4.696, p=0.03] and THC:CBD combination treatment ([QM (df=1)=4.554, p=0.033]. THC-containing CBMs significantly increased incidence of dry mouth, dizziness/ light-headedness and somnolence/drowsiness. Study limitations include inability to fully exclude data from those < 50 years age in our primary analyses as well as limitations related to weaknesses in the included trials particularly incomplete reporting of outcomes and heterogeneity in included studies.

Conclusions: This pooled analysis, using data from RCTs with mean participant age ≥ 50 years, suggests that although THC-containing CBMs are associated with side-effects, CBMs in general are safe and acceptable in older adults. However, THC:CBD combinations may be less acceptable in the dose ranges used and their tolerability may be different in adults over 65 or 75 years of age.

Author summary

Why was this study done?

- Use of cannabinoid-based medicines (CBMs) has been growing steadily in recent years, including in the elderly. However, their safety and tolerability in older adults remains unclear.
- With increasing interest in the use of CBMs in older people and growing unlicensed use, there is a particular need to examine their safety and tolerability in older adults.
- We analysed data on safety and tolerability from previously published double-blind, randomized controlled trials (RCT) using delta-9-tetrahydorcannabinol (THC) and cannabidiol (CBD) the common constituents of most CBMs, alone or in combination, to examine their effect on older adults.

What did the researchers do and find?

- We pooled data from 46 published RCTs (with information from 6216 patients; with mean participant age ≥ 50 years) on adverse events, serious adverse events or death, and withdrawal from study. We also examined the relationship between the dose of THC used in THC-containing CBMs and the incidence of adverse consequences in older adults.
- Our results suggest that compared with the control condition, treatment with THC-containing CBMs was associated on average with significantly greater incidence of all cause and treatment-related adverse events.
- There was no significant increase in the incidence of serious adverse events or death with any CBMs. The risk of withdrawal from study was increased only in those receiving THC:CBD combination treatment, and this was related to THC dose.

What do these findings mean?

- These findings suggest that CBMs in general are safe and acceptable in older adults.

- Our findings that THC-containing CBMs are associated with side-effects and that THC:CBD combinations may be less acceptable at the dose ranges typically used in RCTs is critical to prescribing in older people.

INTRODUCTION

The cannabis plant (CANNABIS SATIVA L.) has been used worldwide both for recreational and medicinal purposes for thousands of years. With a fast-growing aging population, its medicinal use has also caught up and is growing in the elderly [1-3].

Among the cannabinoids found in the cannabis plant, delta-9-tetrahydorcannabinol (THC) and cannabidiol (CBD) are the most well-characterised and often considered for medicinal purposes. THC can cause intoxication [4,5] and has anti-emetic, analgesic and potentially neuroprotective and anti-inflammatory effects. On the other hand, CBD is non- intoxicating [5,6] with antiepileptic and potentially also anti-inflammatory, neuroprotective, antioxidant and antipsychotic effects [7-9]. While several trials have used these cannabinoids for a wide range of diseases and indications, a majority of these have investigated younger people [10,11]. However, age-related pharmacodynamic and pharmacokinetic changes as well as higher prevalence of co-morbidities and polypharmacy in the elderly mean that they may have a different profile of safety and tolerability to cannabinoids [12,13] compared to younger people, as is well-known with other groups of medications especially those used for disorders of the central nervous system [14]. Both THC and CBD, the common constituents of most cannabinoid-based medicines in current use have prominent effects on brain function and cognition [15]. Therefore, evidence of safety and tolerability of cannabinoid-based medicines (CBM) established in studies in younger adults cannot be directly extrapolated to the older adults. Although, a number of recent reviews and meta-analyses [12,16,17] have summarized the safety and tolerability profile of CBMs, they have all pooled data from studies investigating across the age spectrum, making it difficult to draw age-specific inferences. With increasing interest in their use in disorders typically affecting older people [18-20] and growing unlicensed use [21], there is a particular need to investigate the safety and tolerability of CBMs in older people. This is also relevant, as there is a widely held view that many of the naturally derived cannabinoids are generally safe as they have been around and used for a long time.

Here, we have addressed this by investigating the safety and tolerability of CBMs in people over 50 years of age through systematically reviewing all double-blind, randomized controlled trials (RCT) using CBMs that focused on people with mean age of 50 years and over to conduct a meta-analysis. As there is a larger evidence base of studies with mean age of participants ≥ 50 years than the more limited set of studies that have exclusively focused on people over 50 years and even less on people over 65 or 75 years, we have focused on studies with mean age of participants ≥ 50 years and complemented these results with additional analyses restricted to studies that have exclusively focused on people over 50 years and even less on people over 65. Existing meta-analytic investigations [16,17] have generally considered all CBMs together, irrespective of whether they included THC, CBD or THC:CBD in combination. However, THC can cause intoxication and may induce anxiety and transient psychotomimetic effects [5], especially at higher doses and in vulnerable individuals, while CBD does not cause intoxication when directly compared in the same individuals [5] and may potentially ameliorate anxiety and psychosis [9,22-24]. Further, there is growing evidence that THC and CBD may have opposing acute effects on autonomic arousal, brain [15] and cardiovascular function [25,26] and CBD may mitigate some of the harmful effects of THC on cognition and behaviour [15,27,28], consistent with their opposing effects on some of their molecular targets [4]. This suggests that THC and CBD may have distinct tolerability profiles, with the possibility that certain side-effects may be noticeable in those taking formulations containing only THC, but not in those taking formulations containing only CBD while adverse effects may even be mitigated in those taking THC and CBD in combination. This underscores the importance of examining their safety and tolerability separately. Therefore, we have addressed this issue by separately investigating the effects of THC, CBD or THC:CBD in combination.

We hypothesized that compared to control treatments all 3 categories of CBMs will be associated with: i) a greater incidence of adverse events (AEs); ii) no greater incidence of

serious adverse events (SAEs) or death; and iii) no greater risk of withdrawal from study. Further, we hypothesized a direct relationship between the dose of THC used in THC-containing CBMs and the incidence of adverse consequences in older adults.

METHODS

Data sources and searches

The review was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines [29] (see S1 PRISMA checklist). The study protocol was pre-registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42019148869). Ethics approval was not required for this systematic review and meta-analysis.

A detailed description of the bibliographic search strategy is presented in Methods in S2 appendix. We identified studies published from Jan 1, 1990 up to 31st Oct 2020, from several electronic databases. Studies were independently assessed by 2 researchers and disagreements resolved through consensus or discussions with a third researcher.

Study selection

Studies were included if (1) published from 1990 onwards; (2) included older adults (defined as mean age ≥50 years) or reported a distinct subgroup of older adults and provided separate results for this subgroup; and (3) provided data on the safety and tolerability of medical cannabinoids administered by any route, at any dose, for any duration and for any indication. Studies were excluded if they (1) included exclusively younger subjects (mean age <50 years); (2) studied effects of cannabinoids for recreational purposes or failed to provide the dosage of cannabinoids; and (3) were not reported in English language. Here we focus on results from randomised controlled trials (RCTs).

Data extraction and quality assessment

All relevant available data for examination of the safety and tolerability of different CBMs (THC:CBD combination or THC or CBD alone) was collected from eligible studies, complemented with information from ClinicalTrials.gov and author responses.
Data was extracted for study design, participant characteristics, indication, dosage and duration of intervention, all cause and treatment-related AEs and SAEs, AE-related withdrawals and deaths.

AEs and SAEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) 'system organ classes' (SOC). Data was also extracted for the top 5 (as reported by each study) AEs for each SOC, where available. Data extraction and coding was verified by a medically qualified researcher and discrepancies resolved following discussions with senior researcher. The disease conditions investigated were classified into broader subgroups for analysis purpose.
Overall quality of evidence was assessed using recommended criteria [30] and summarised to reflect confidence in estimates [31].

Data synthesis and analysis

Total exposure to active intervention in person-years was estimated by first calculating this for each individual study by multiplying the number of subjects in the active intervention arm with the duration of treatment for that arm for each study and then adding up these study-specific values for all studies under each broad category (THC, THC:CBD or CBD) of intervention investigated here. Mean exposure in person-years for each category (THC, THC:CBD or CBD) of intervention was estimated by calculating the arithmetic mean from study-specific estimates obtained as above for each intervention category. Pooled mean ages of participants for each group of studies and treatment arms were estimated by calculating the arithmetic mean of study specific mean age as reported by individual studies for each intervention arm. Other pooled estimates (median and interquartile range) for summary study characteristics , such as, duration of study in weeks, participants analysed or

included, or duration of treatment for each treatment arm (as reported in Table 1 in S2 Appendix), were calculated by estimating them from the total number (e.g. for variables such as number of participants included or analysed; duration of study or treatment) or the mean estimate (e.g. for variables such as mean age) as reported in individual studies for each set sub groups of RCTs.

Pooled effect-sizes were estimated if there were 2 or more RCTs within each group or sub-group under the random-effects model using the restricted maximum-likelihood estimator because of anticipated heterogeneity. For each broad category of intervention, analyses combined both parallel-arm and crossover RCTs, with the latter treated as parallel-arm design [32] for pooled analyses. But we also report results by RCT design for each intervention. We estimated incident rate ratio (IRR) for outcome data such as AEs, SAEs and death and risk ratio (RR) for withdrawal from study. Studies with more than one active treatment arm were treated as independent studies. In studies with more than one active treatment arm compared against a single control group we also report meta-analysis of dependent effect-sizes with robust variance estimation [33-35]. For the purpose of reporting throughout the manuscript, results are reported for analyses treating all studies as independent, while corresponding dependent meta-analyses are reported in Appendix Results and signposted in the main text as appropriate. We investigated heterogeneity using forest plots and the I^2 statistic and publication bias using Egger's regression test [36] and the 'Trim and fill' method [37]. For the analysis of AEs, data for all conditions were combined. We also examined whether estimates varied according to treatment, design, clinical condition and dose of study drug using meta-regression.

Our primary analysis includes the results of all studies where the mean age of study participants was ≥50 years. As many participants in these included studies were <50 years of age, we also carried out separate analyses restricted to studies where all participants were ≥ 50 years of age and also where all participants were ≥ 65 years of age. These

analyses were carried out where there were at least 2 studies with analysable data. Statistical analyses were performed using the metafor package in R (version 3.6.3) [38]. For meta-analysis of dependent effect-sizes with robust variance estimation we also used the *clubSandwich* package (https://github.com/jepusto/clubSandwich) along with *metafor* in R.

RESULTS

Data selection

Figure 1 (PRISMA flow chart) summarizes the study selection procedure. Main characteristics and outcome measures of each study are included in Table 1A, 1B and 1C; additional details regarding studies are presented in Results in S2 Appendix and Tables 2a-b in S2 Appendix. A total of 60 comparisons of CBM and control intervention using RCT design (hereafter called RCTs) (n= 6216 participants; 1933.47person-years of cannabinoid exposure) from 46 published articles were included (Figure 1). Of these, 4 RCTs recruited participants over age ≥ 65 years (n=68; mean age, 72.4 (SD± 4.5)), of which one was ≥ 75 years (Table 1a and b) [39-42].

Figure 1. Study disposition

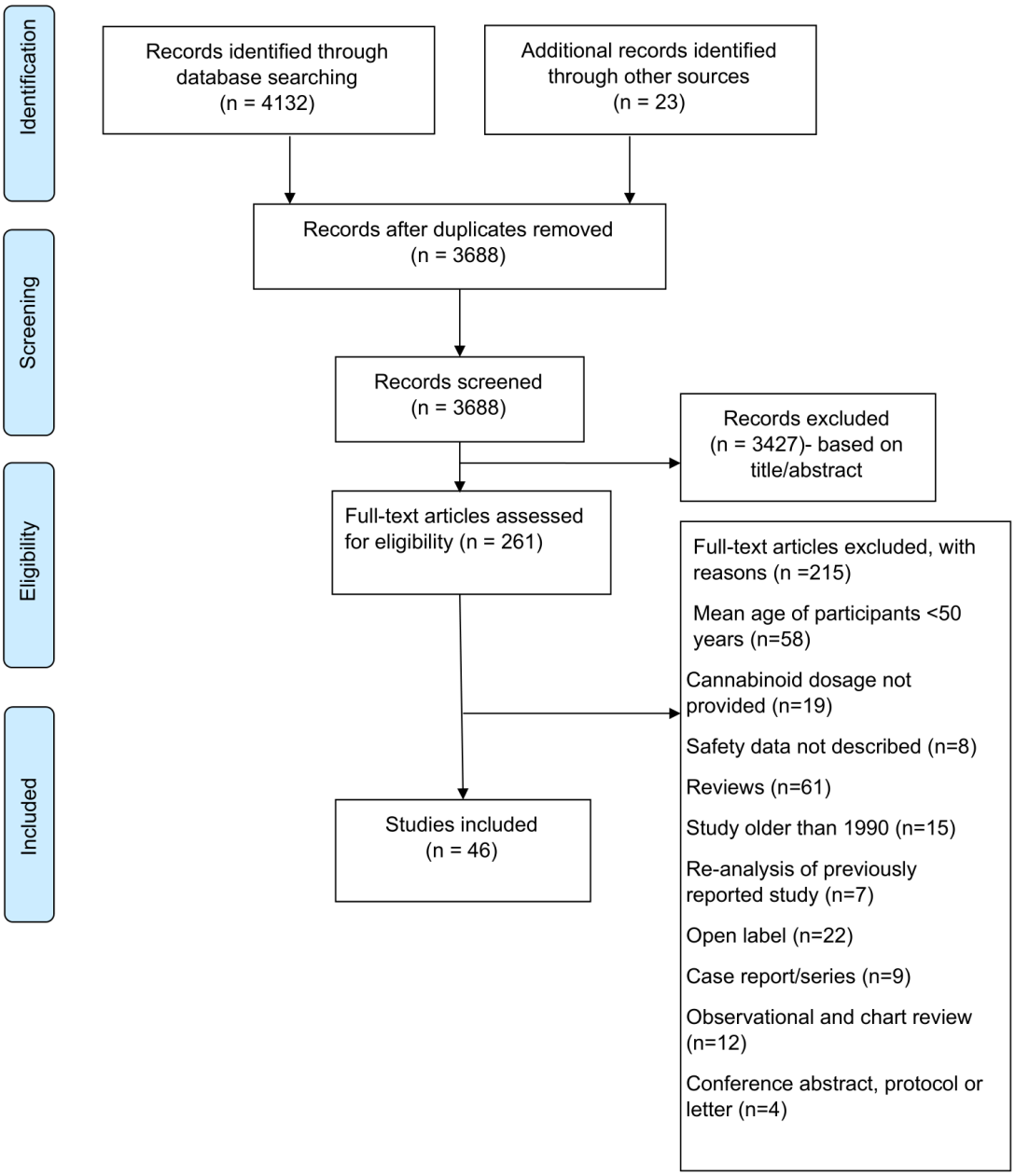


Table 1a: Characteristics of included randomised controlled trials of THC in older adults (N=30)

Study ID (country)	Study Design (RCT)	THC: Sample included/analysed N Mean age (SD), Male %	Comparator: Sample included/analysed N Mean age (SD), Male %	Age cut-off for enrolment	Indication	THC classification	Comparator	THC treatment duration, weeks	Calculated daily average THC dose	Overall GRADE rating for study
***Ahmed et al. 2014, (Netherlands)	Crossover	12/11 72.00 (5), 50	12/11 72.00 (5), 50	≥65 years	Healthy older subjects	Namisol	Placebo	.4	6.5mg	Moderate
Ahmed et al. 2015 (Netherlands)	Crossover	10/10 77.30 (5.6), 70	10/10 77.30 (5.6), 70	≥18 years	Dementia	Namisol	Placebo	2.6	3 mg	Moderate
Brisbois et al. 2011 (Canada)	Parallel-arm	24/11 67.00 (10.9), 64	22/10 65.50 (8), 50	Adult	Cancer patients with chemosensory alterations	Dronabinol	Placebo	2.6	7.5 mg	Low
Carley et al. 2018 (USA) ‡	Parallel-arm	21/21 52.70 (7.7), 76	25/25 58.80 (6.1), 72	21-65 years	Obstructive Sleep Apnoea	Dronabinol	Placebo	6.0	2.5 mg	Low
Carley et al. 2018 (USA) ‡	Parallel-arm	27/27 54.70 (7), 67	25/25 58.80 (6.1), 72	21-65 years	Obstructive Sleep Apnoea	Dronabinol	Placebo	6.0	10 mg	Low
Curtis et al. 2009 (UK)	Crossover	44/37 52.00 (9.5), 50	44/37 52.00 (9.5), 50	≥18 years	Huntington's disease	Nabilone	Placebo	5.0	2 mg	Low
De Vries et al. 2016 (Netherlands)	Crossover	25/24 52.00 (NR), 62	25/24 52.00 (NR), 62	>18 years	Chronic pancreatitis	Namisol	Diazepam	.1	8 mg	Moderate
**Herrmann et al. 2019, (Canada)	Crossover	39/38 87.00 (10), 77	39/38 87.00 (10), 77	≥55 years	Alzheimer's disease	Nabilone	Placebo	6.0	1.6 mg	Moderate
Jatoi et al. 2002 (USA)	Parallel-arm	152/152 67.00 (10), 66	159/159 65.00 (11), 65	≥18 years	Cancer-related anorexia	Dronabinol	Megestrol acetate	8.1	5 mg	Low
Johnson et al. 2010 (UK) §	Parallel-arm	58/58 61.30 (12.5), 52	59/59 60.10 (12.3), 54	NR	Patients with cancer-related pain	THC extract spray	Placebo	2.0	23 mg	Moderate
Lane et al. 1991 (USA)	Parallel-arm	21/21 47.0 (20-68) *,† 48	21/21 49.0 (22-64) *,† 48	18-69 years	Chemotherapy-induced nausea and vomiting	Dronabinol	Prochlorperazine	.9	40 mg	Low
Meiri et al. 2007 (USA)	Parallel-arm	17/17 61.60 (14.2), 53	14/14 57.20 (8.6), 38	≥18 years	Chemotherapy-induced nausea and vomiting	Dronabinol	Placebo	.7	20 mg	Low
Peball et al. 2020 (Austria)	Parallel-arm	19/19 65.4 (7.94), 53	19/19 64.0 (8.04), 74	≥30 years	Parkinson's disease	Nabilone	Placebo	4.0	0.75 mg	Moderate
Sieradzan et al. 2001(UK)	Crossover	9/9 59.00 (NR), 44	9/9 59.00 (NR), 44	NR	Parkinson's disease	Nabilone	Placebo	.1	2 mg	Very low
Strasser et al. 2006	Parallel-arm	100/100 60.00 (12), 54	48/48 62.00 (10), 52	Adult	Cancer-related anorexia	THC	Placebo	6.0	5 mg	Low

(Germany) [§]										
Svendsen et al. 2004 (Denmark)	Crossover	24/24 50.0 (NR), 42	24/24 50.0 (NR), 42	18-55 years	Multiple sclerosis	Dronabinol	Placebo	3.0	10 mg	Moderate
Tomida et al. 2006 (UK) [§]	Crossover	6/6 55.30 (5), 100	6/6 55.30 (5), 100	NR	Intraocular pressure	THC extract spray	Placebo	.1	5 mg	Low
Toth et al. 2012 (Canada)	Parallel-arm	13/13 60.80 (15.3), 38	13/13 61.60 (14.6), 69	18-80	Diabetic peripheral neuropathic pain	Nabilone	Placebo	5.0	4 mg	Low
Van Amerongen et al. 2017, 2 (Netherlands) [ll]	Crossover	24/24 54.30 (8.9), 33	24/24 54.30 (8.9), 33	≥18 years	Multiple sclerosis	THC	Placebo	.1	16 mg	Moderate
Van Amerongen et al. 2017, 1 (Netherlands) [ll]	Parallel-arm	12/12 57.30 (9), 33	12/12 51.40 (8), 33	≥18 years	Multiple sclerosis	THC	Placebo	4.0	28.5 mg	Moderate
Van den Elsen et al. 2015, 1 (Netherlands)	Parallel-arm	24/24 79.00 (8), 46	26/26 78.00 (7), 54	≥40 years	Dementia	Namisol	Placebo	3.0	4.5 mg	Moderate
Van den Elsen et al. 2015, 2 (Netherlands)	Crossover	22/22 76.40 (5.3), 68	22/22 76.40 (5.3), 68	≥18 years	Dementia	Namisol	Placebo	2.6	3 mg	Moderate
***Volicer et al. 1997 (USA)**	Crossover	15/12 72.70 (4.9), 92	15/12 72.70 (4.9), 92	NR	Alzheimer's disease	Dronabinol	Placebo	6.0	5 mg	Very low
***Walther et al. 2011 (Switzerland)**	Crossover	2/2 78.00 (NR), 100	2/2 78.00 (NR), 100	NR	Alzheimer's disease	Dronabinol	Placebo	2.0	2.5 mg	Very low
Ware et al. 2010 (Canada)	Crossover	32/32 50.00 (11.2), 16	32/32 50.00 (11.2), 16	≥18 years	Fibromyalgia	Nabilone	Amitriptyline	2.0	1 mg	Moderate
Weber et al. 2010 (Switzerland)	Crossover	27/22 57.00 (12), 74	27/22 57.00 (12), 74	Adult	Amyotrophic lateral sclerosis patients with cramps	Dronabinol	Placebo	2.0	10 mg	Moderate
Zadikoff et al. 2011 (Canada)	Crossover	9/9 60.00 (7), 0	9/9 60.00 (7), 0	18-75	Cervical dystonia	Dronabinol	Placebo	3.0	15 mg	Low
Zajicek et al. 2003 (UK) [§]	Parallel-arm	216/206 50.00 (8.2), 31	222/213 51.00 (7.6), 37	18-64	Multiple sclerosis	Dronabinol	Placebo	14.0	25mg	Moderate
Zajicek et al. 2005 (UK) [§]	Parallel-arm	125/125 50.00 (8.2), 31	120/120 51.00 (7.6), 37	18-64	Multiple sclerosis	Dronabinol	Placebo	52.0	25 mg	Moderate
Zajicek et al. 2013 (UK)	Parallel-arm	332/329 52.30 (7.6), 40	166/164 52.00 (8.2), 41	18-65	Multiple sclerosis	Dronabinol	Placebo	160.0	28 mg	Moderate

Table 1b: Characteristics of included randomised controlled trials of THC:CBD combination in older adults (N=24)

Study ID (country)	Study Design	CBD/THC: Sample included/analysed N Mean age (SD), Male %	Comparator: Sample included/analysed N Mean age (SD), Male %	Age cut-off for enrolment	Indication	CBD/THC classification	Comparator	CBD/THC treatment duration, weeks	Calculated daily average CBD/THC dose	GRADE rating
Blake et al. 2006 (UK)	Parallel-arm	31/31 60.9 (10.6), 26	27/27 64.9 (8.5), 15	NR	Rheumatoid arthritis	THC:CBD spray	Placebo	5.0	14.6mg THC: 13.5mg CBD	Low
****Carroll et al. 2004 (UK)**	Crossover	19/17 67.0 (NR) 63	19/17 67.0 (NR) 63	18-78 years	Levodopa induced dyskinesia in Parkinson's disease	Cannabis extract	Placebo	4.0	10.2mg THC: 5.1mg CBD	Moderate
Duran et al. 2010 (Spain)	Parallel-arm	7/7 50 (41-70) * 0	9/9 50 (34-76) * 11	>18 years	Chemotherapy induced nausea and vomiting	THC:CBD spray	Placebo	.6	13mg THC : 12mg CBD	Moderate
Fallon et al. 2017, 1 (Multicentre) ‖	Parallel-arm (withdrawal study)	103/103 61.4 (10.9), 61	103103 61.6 (11.8), 53	≥18 years	Advanced cancer patients with pain	THC:CBD spray	Placebo	5.0	17.6mg THC: 16.3mg CBD	Moderate
Fallon et al. 2017, 2 (Multicentre) ‖	Parallel-arm	200/199 60.0 (11), 53	199/198 59.6 (11), 49	≥18 years	Advanced cancer patients with pain	THC:CBD spray	Placebo	5.0	17mg THC: 15.8mg CBD	Moderate
Jadoon et al. 2016, 1 (UK) ‡,§	Parallel-arm	11/11 59.0 (8.8), 55	14/14 59.0 (7.7), 50	≥18 years	Type 2 diabetes	CBD/THCV	Placebo	13.0	10mg THC: 10mg CBD	Moderate
Jadoon et al. 2016, 2 (UK) ‡,§	Parallel-arm	12/12 58.0 (8.1), 75	14/14 59.0 (7.7), 50	≥18 years	Type 2 diabetes	CBD/THCV	Placebo	13.0	10mg THC: 200mg CBD	Moderate
Johnson et al. 2010, **(UK)** §	Parallel-arm	60/60 59.4 (12.1), 55	59/59 60.1 (12.3), 54	NR	Patients with cancer-related pain	THC:CBD spray	Placebo	2.0	25mg THC: 23mg CBD	Moderate

Litchman et al. 2018, (Multicentre)	Parallel-arm	199/199 59.2 (12), 56	198/198 60.7 (11.1), 52	≥18 years	Advanced cancer patients with pain	THC:CBD spray	Placebo	5.0	17.3mg THC: 16mg CBD	Moderate
Lynch et al. 2014 (USA)	Crossover	18/16 56.0 (10.8), 17	18/16 56.0 (10.8), 17	NR	Chemotherapy-induced neuropathic pain	THC:CBD spray	Placebo	6.0	21.6mg THC: 20mg CBD	Low
Markova et al. 2019, (Czech Republic)	Parallel-arm	53/53 51.3 (10.2) 30	53/53 51.3 (10.2) 30	≥18 years	Multiple sclerosis	THC:CBD spray	Placebo	12.0	19.7mg THC: 18.3mg CBD	Low
Notcutt et al. 2012 (UK)	Parallel-arm (withdrawal study)	18/18 59.7 (9) 50	18/18 54.4 (10.4) 33	NR	Multiple sclerosis	THC:CBD spray	Placebo	4.0	20.8mg THC: 19.3mg CBD	Very low
Nurmikko et al. 2007, (UK)	Parallel-arm	63/63 52.4 (15.8), 44	62/62 54.3 (15.2), 37	≥18 years	Neuropathic pain	THC:CBD spray	Placebo	5.0	THC 29.7mg: CBD 27.5mg	High
***Pickering et al. 2011, 1 (UK) ¶	Crossover	5/4 67.0 (NR), 50	5/4 67.0 (NR), 50	40-74 years	COPD	THC:CBD spray	Placebo	.1	4.7mg THC: 4.4mg CBD	Low
**Pickering et al. 2011, 2 (UK) ¶	Crossover	6/5 58.0 (NR), 80	6/5 58.0 (NR), 80	40-75 years	Healthy controls	THC:CBD spray	Placebo	.1	10.3mg THC: 9.5mg CBD	Low
Portenoy et al. 2012, 1 (Multicentre) ‡	Parallel-arm	91/91 59.0 (12.3), 49	91/91 56.0 (12.2), 48	NR	Cancer patients with chronic pain	THC:CBD spray	Placebo	5.0	10.8mg THC: 10mg CBD	Moderate
Portenoy et al. 2012, 2 (Multicentre) ‡	Parallel-arm	88/87 59.0 (13.1), 56	91/91 56.0 (12.2), 48	NR	Cancer patients with chronic pain	THC:CBD spray	Placebo	5.0	27mgTHC: 25mg CBD	Moderate

Portenoy et al. 2012, 3 (Multicentre) ‡	Parallel-arm	90/90 58.0 (11.2), 53	91/91 56.0 (12.2), 48	NR	Cancer patients with chronic pain	THC:CBD spray	Placebo	5.0	43.2mg THC: 40mg CBD	Moderate
Riva et al. 2019 (Italy)	Parallel-arm	30/29 58.4 (10.6) 62	30/30 57.2 (13.8) 53	18-80 years	Motor neurone disease	THC:CBD spray	Placebo	6.0	21.6mg THC: 20.0mg CBD	High
Serpell et al. 2014, (UK)	Parallel-arm	128/128 57.6 (14.4), 34	118/118 57.0 (14.1), 45	≥18 years	Neuropathic pain	THC:CBD spray	Placebo	14.0	24mg THC: 22mg CBD	Moderate
Strasser et al. 2006 (Germany) §	Parallel-arm	95/95 61.0 (12), 56	48/48 62.0 (10), 52	Adult	Cancer-related anorexia	Cannabis extract	Placebo	6.0	5mg THC: 2mg CBD	Moderate
Vaney et al. 2004 (Switzerland)	Crossover	57/50 55.0 (10), 49	57/50 55.0 (10), 49	Adult	Multiple sclerosis	Cannabis extract	Placebo	2.0	27.5mg THC: 9.9mg CBD	Low
Wade et al. 2004 (UK)	Parallel-arm	80/80 51.0 (9.4), 41	80/80 50.0 (9.3), 35	NR	Multiple sclerosis	THC:CBD spray	Placebo	6.0	40.5mg THC: 37.5mg CBD	Moderate
Zajicek et al. 2003, (UK) §	Parallel-arm	219/211 51.0 (7.6), 36	222/213 51.0 (7.6), 37	18-64 years	Multiple sclerosis	Cannabis extract	Placebo	14.0	25mg THC: 12.5mg CBD	Moderate
Zajicek et al. 2005, (UK) §	Parallel-arm	138/138 51.0 (7.6), 36	120/120 51.0 (7.6), 37	18-64 years	Multiple sclerosis	Cannabis extract	Placebo	52.0	25mg THC: 12.5mg CBD	Moderate
Zajicek et al. 2012, (UK)	Parallel-arm	144/143 51.9 (7.7), 39	135/134 52.0 (7.9), 35	18-64 years	Multiple sclerosis	Cannabis extract	Placebo	12.0	25mg THC: 12.5mg CBD	Moderate

Table 1c: Characteristics of randomised controlled trials of CBD in older adults (N=4)

Study ID (country)	Study Design	CBD: Sample included/analysed N Mean age (SD) Male %	Comparator: Sample included/analysed N Mean age (SD) Male %	Age cut-off for enrolment	Indication	Active treatment	Comparator	CBD treatment duration, weeks	Calculated daily average CBD dose	GRADE rating
Consroe et al. 1991, USA	Crossover	18/15 47.8[2] (15.3), 53	18/15 47.8[2] (15.3), 53	NR	Huntington's Disease	CBD	Placebo	6	700mg	Low
Jadoon et al. 2016[§] UK	Parallel-arm	13/13 56.8 (9.9), 77	14/14 59.0 (9.4) 68	≥18 years	Type 2 diabetes	CBD	Placebo	13	200mg	Moderate
Tomida et al. 2006[‡,§] UK	Crossover	6/6 55.3 (5.0), 100	6/6 55.3 (5.0), 100	NR	Intraocular pressure	CBD	Placebo	0.1	20mg	Low
Tomida et al. 2006 [‡,§] UK	Crossover	6/6 55.3 (5.0), 100	6/6 55.3 (5.0), 100	NR	Intraocular pressure	CBD	Placebo	0.1	40mg	Low

*, Median age (range); †, Included as median age for whole study population was ≥50; ‡, Article included more than one dose level; §, Article included more than one cannabinoid intervention; ||, Article included the results of multiple trials; ¶, Article included multiple study groups/indications ; NR, Not recorded

**Studies recruited participants ≥50years; ***Studies recruited participants ≥65 years

The formulations used in THC studies were (numbers within brackets indicating the number of RCTs where each formulation was used): nabilone (6), dronabinol (marinol) (14), THC (3), THC extract spray (2) and Namisol (5). The combination THC:CBD trials used THC:CBD spray (18), cannabis extract (6) and CBD/THCV (2). The CBD studies used CBD preparations only.

The disease conditions investigated were classified into broader subgroups for analysis purpose as neurodegenerative (Alzheimer's disease, Parkinson's disease, Huntington's disease. Amyotrophic lateral sclerosis), multiple sclerosis, motor neuron disease, pain (neuropathic pain), cancer (cancer or chemotherapy related anorexia, pain or nausea/vomiting), other (type 2 diabetes mellitus, chronic obstructive pulmonary disease, fibromyalgia, raised intraocular pressure, cervical dystonia, healthy, pancreatitis, obstructive sleep apnoea and Levodopa induced dyskinesia in Parkinson's disease).

Figures 2 (A-F), figures 3 (A-F) and Figure 4A show the forest-plots and summary results of the meta-analyses stratified according to study design, for all cause and treatment-related AEs and SAEs, withdrawals, deaths, for studies using THC, THC:CBD combination and CBD respectively.

Figure 2A. Forest Plot of all cause Adverse Events: THC studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively.

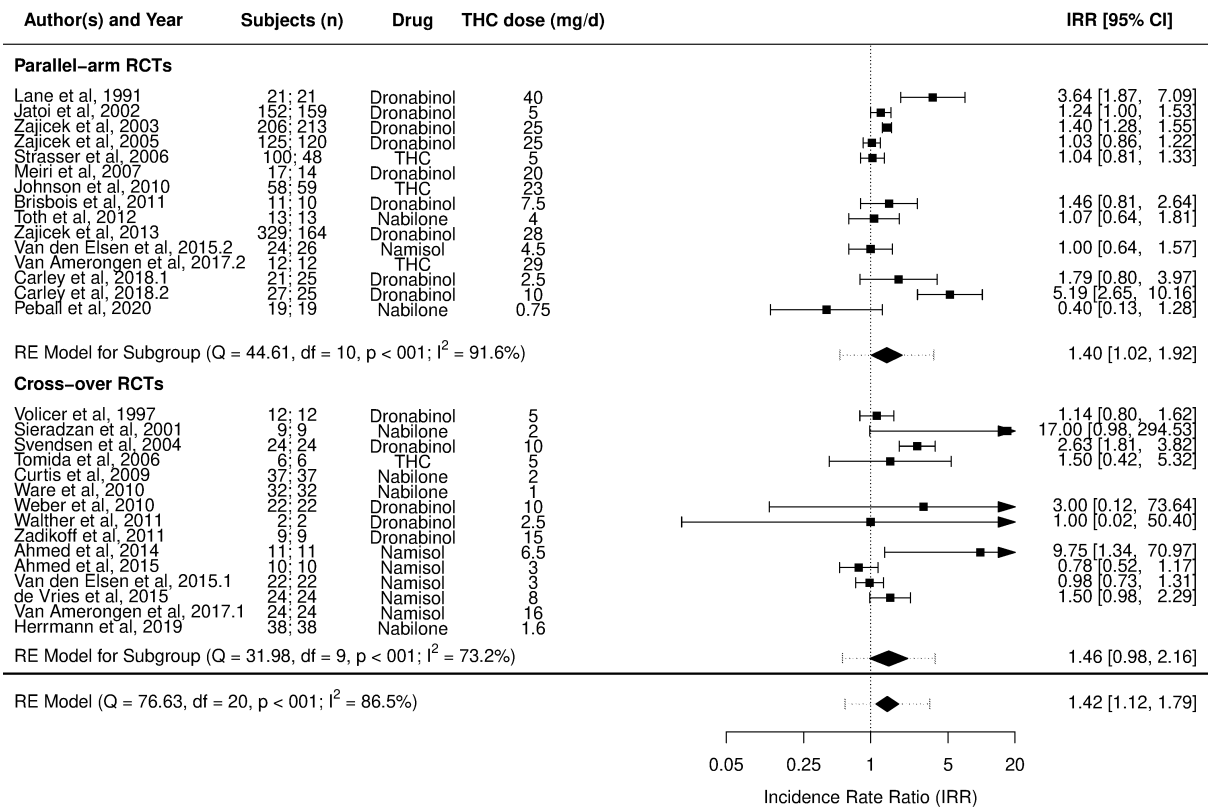


Figure 2B. Forest Plot of treatment-related Adverse Events: THC studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively.

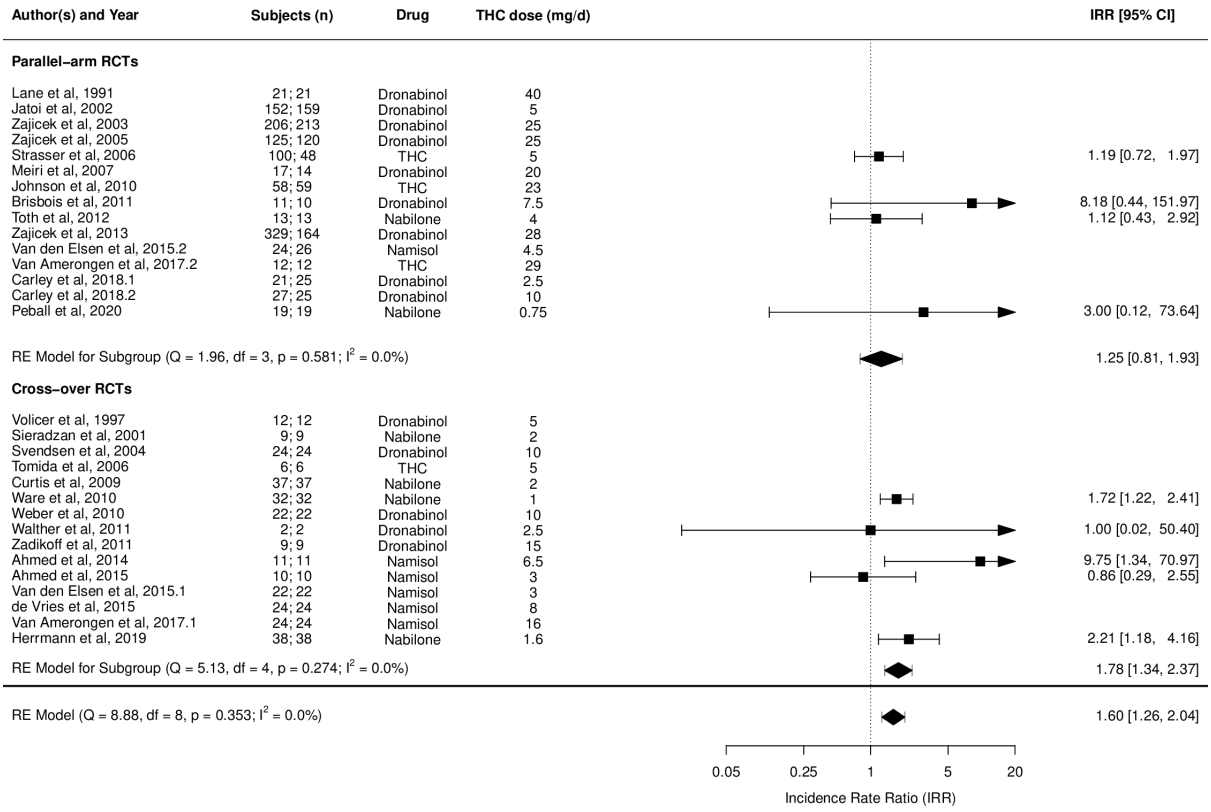


Figure 2C. Forest Plot of all cause Serious Adverse Events: THC studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively.

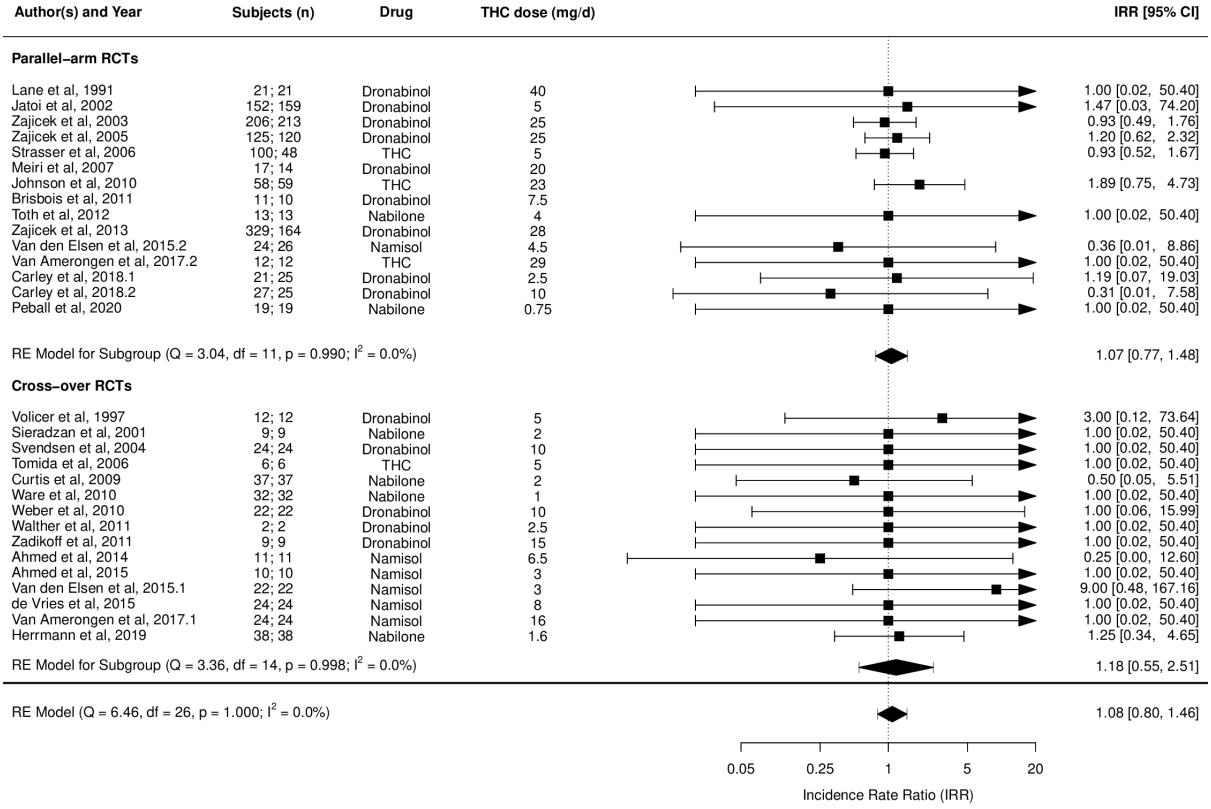


Figure 2D. Forest Plot of treatment-related Serious Adverse Events: THC studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively.

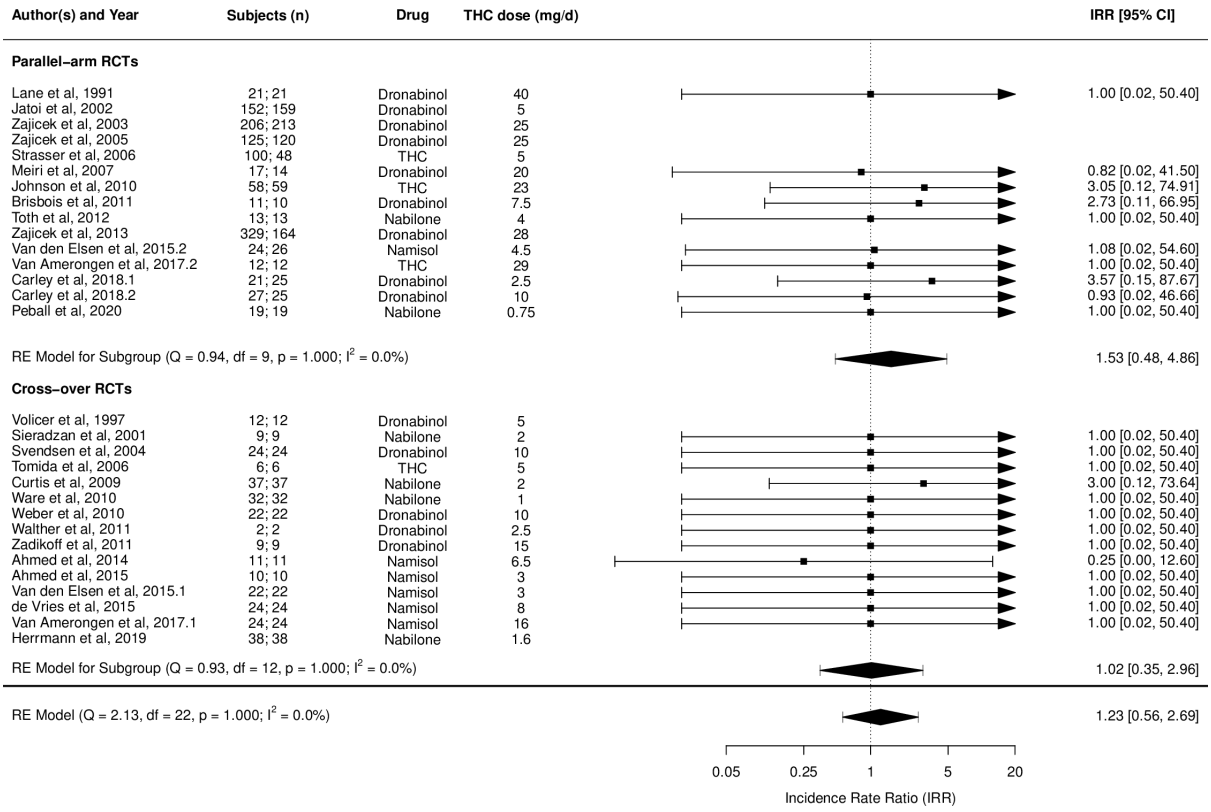
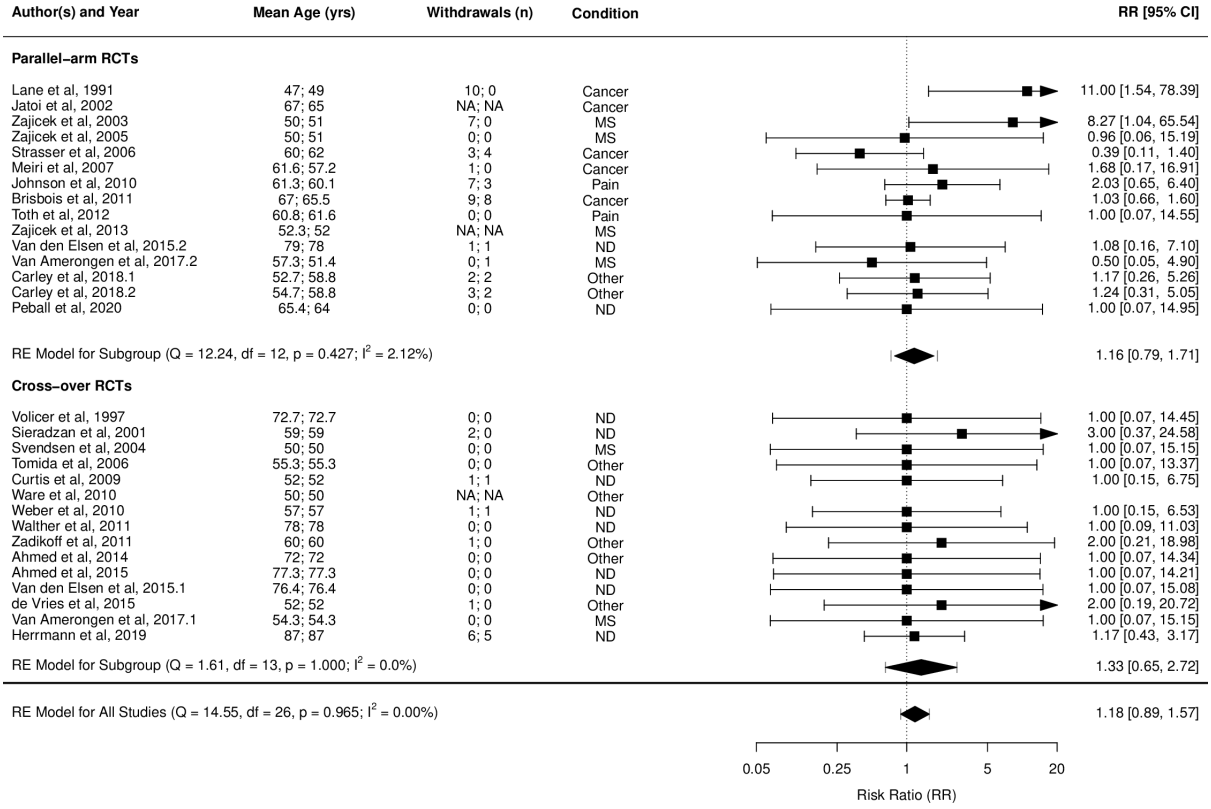


Figure 2E. Forest Plot of Adverse Event-related Withdrawals: THC studies.

Numbers under the 'Mean Age (yrs)' and 'Withdrawals (n)' columns refer to the values in active and control intervention arms respectively.



The conditions listed are the disease conditions sub-grouped into broader categories for meta-regression analyses purposes. They are: Neurodegenerative disorders (ND) (dementia, Alzheimer's disease, Parkinson's disease (PD), Huntington's disease, Amyotrophic lateral sclerosis); Multiple sclerosis (MS); Cancer (cancer or chemotherapy related anorexia, pain or nausea/vomiting, chemosensory alterations); and Other (type 2 diabetes mellitus, fibromyalgia, raised intraocular pressure, cervical dystonia, healthy, pancreatitis, obstructive sleep apnoea).

Figure 2F. Forest Plot of all deaths: THC studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively.

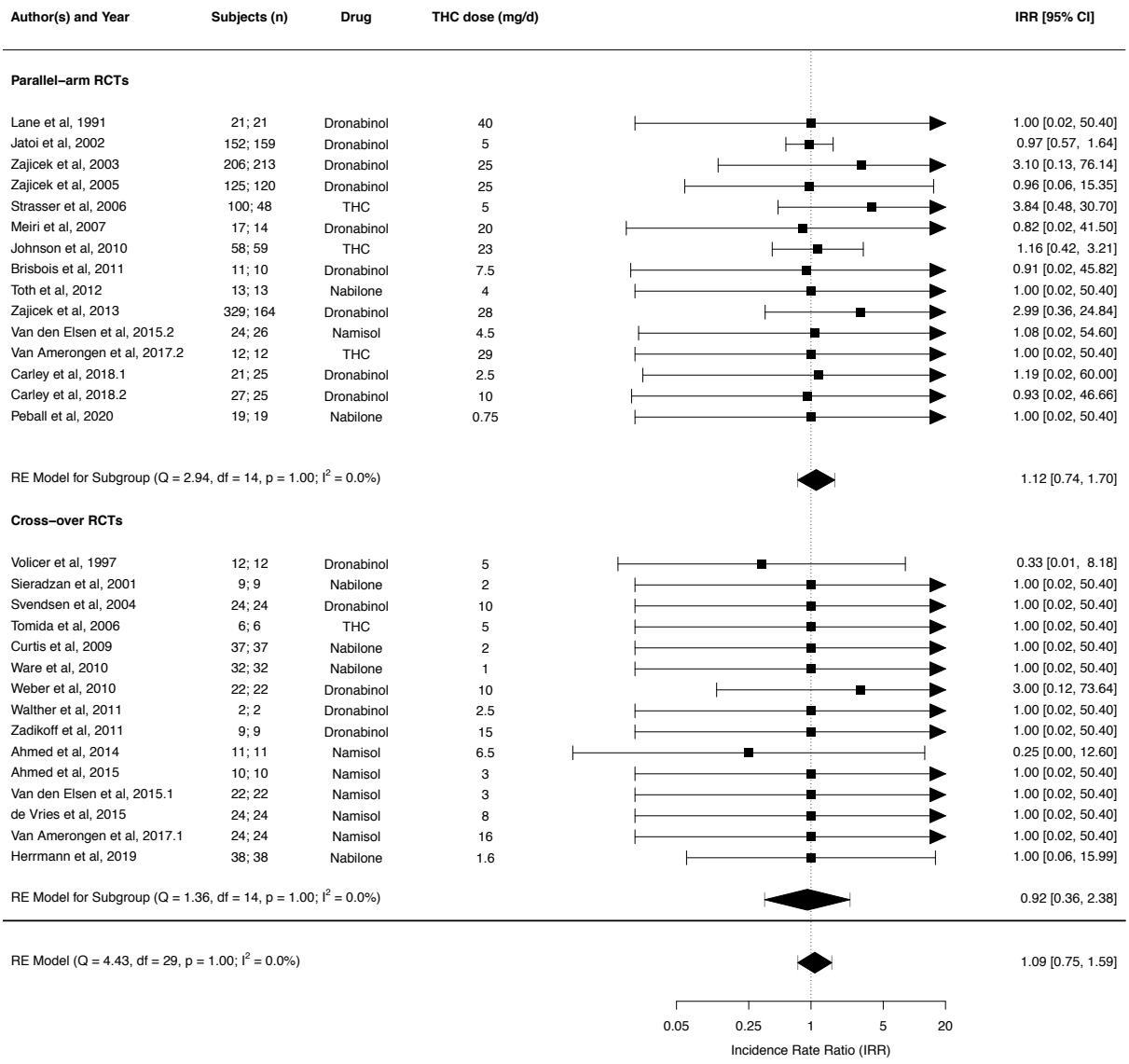


Figure 3A. Forest Plot of all cause Adverse Events: THC:CBD studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively. *CE* refers to cannabis extract.

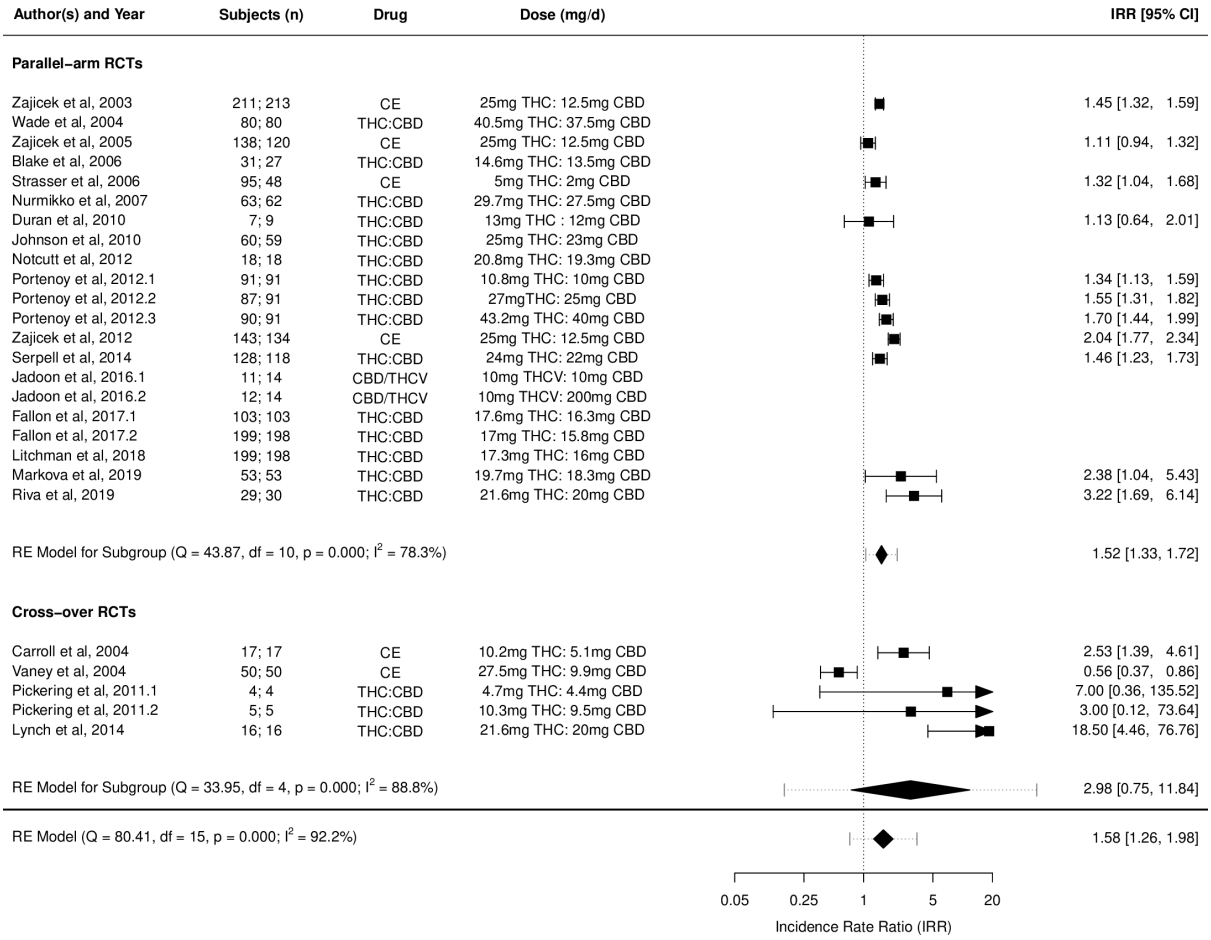


Figure 3B. Forest Plot of treatment-related Adverse Events: THC:CBD studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively. *CE* refers to cannabis extract.

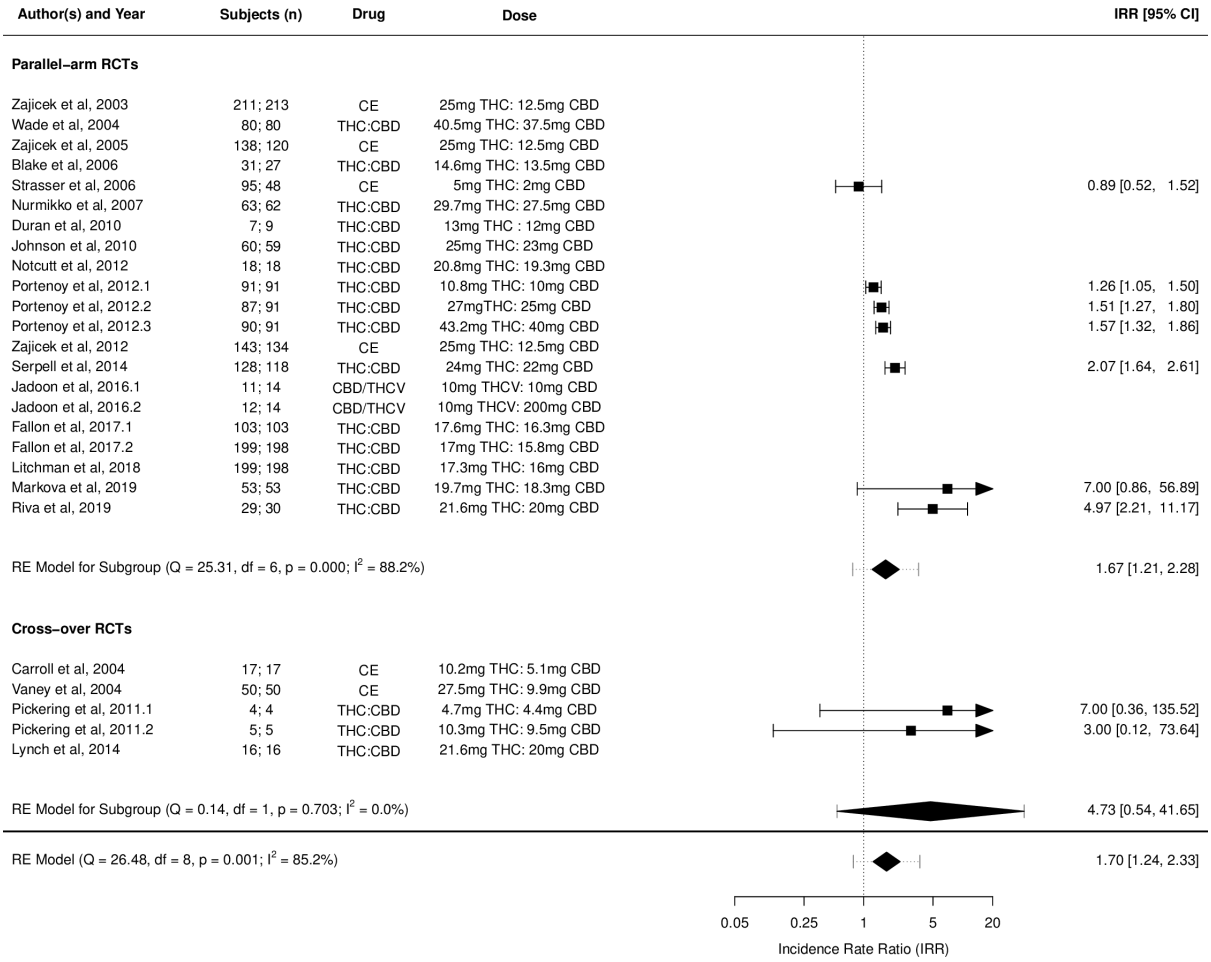


Figure 3C. Forest Plot of all cause Serious Adverse Events: THC:CBD studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively. *CE* refers to cannabis extract.

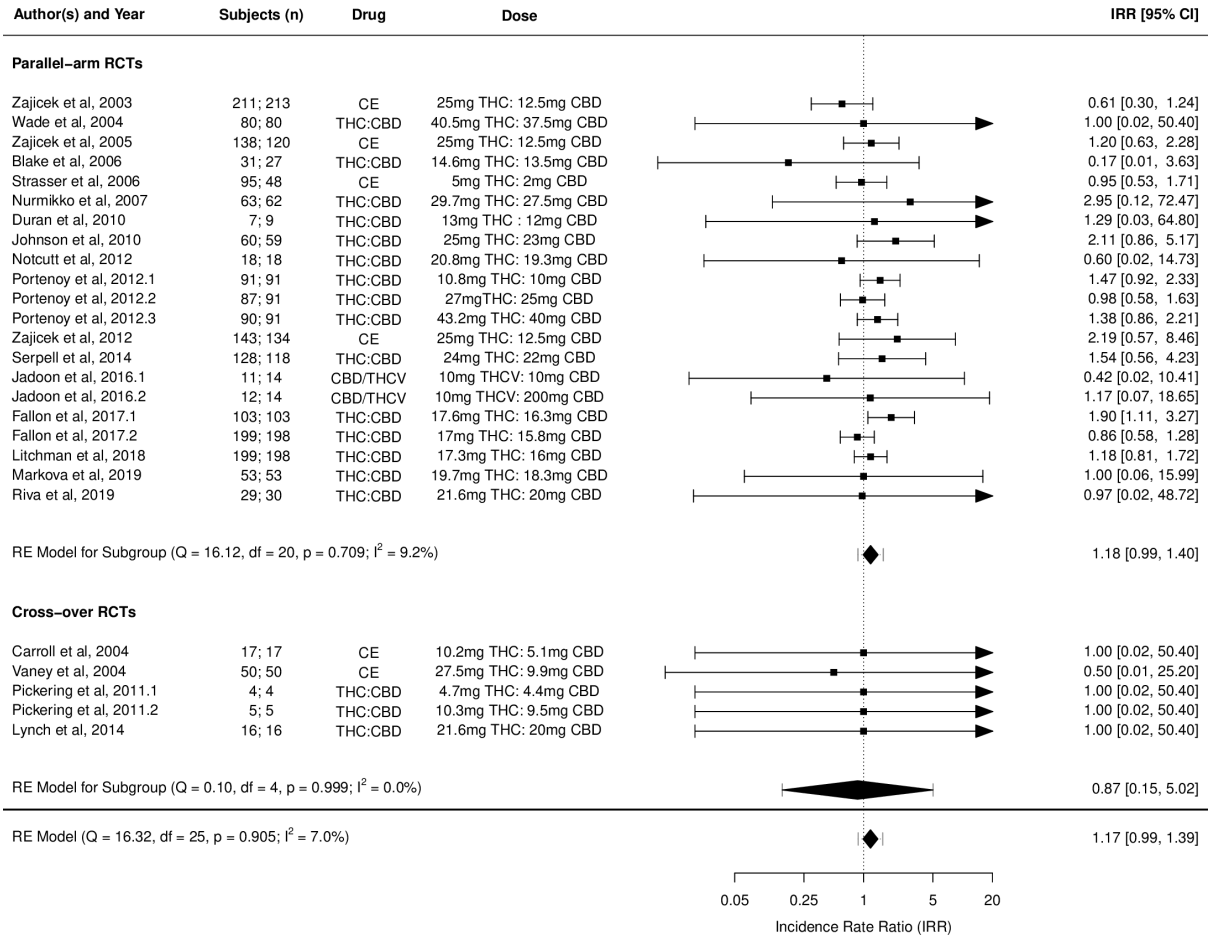


Figure 3D. Forest Plot of treatment-related Serious Adverse Events: THC:CBD studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively. *CE* refers to cannabis extract.

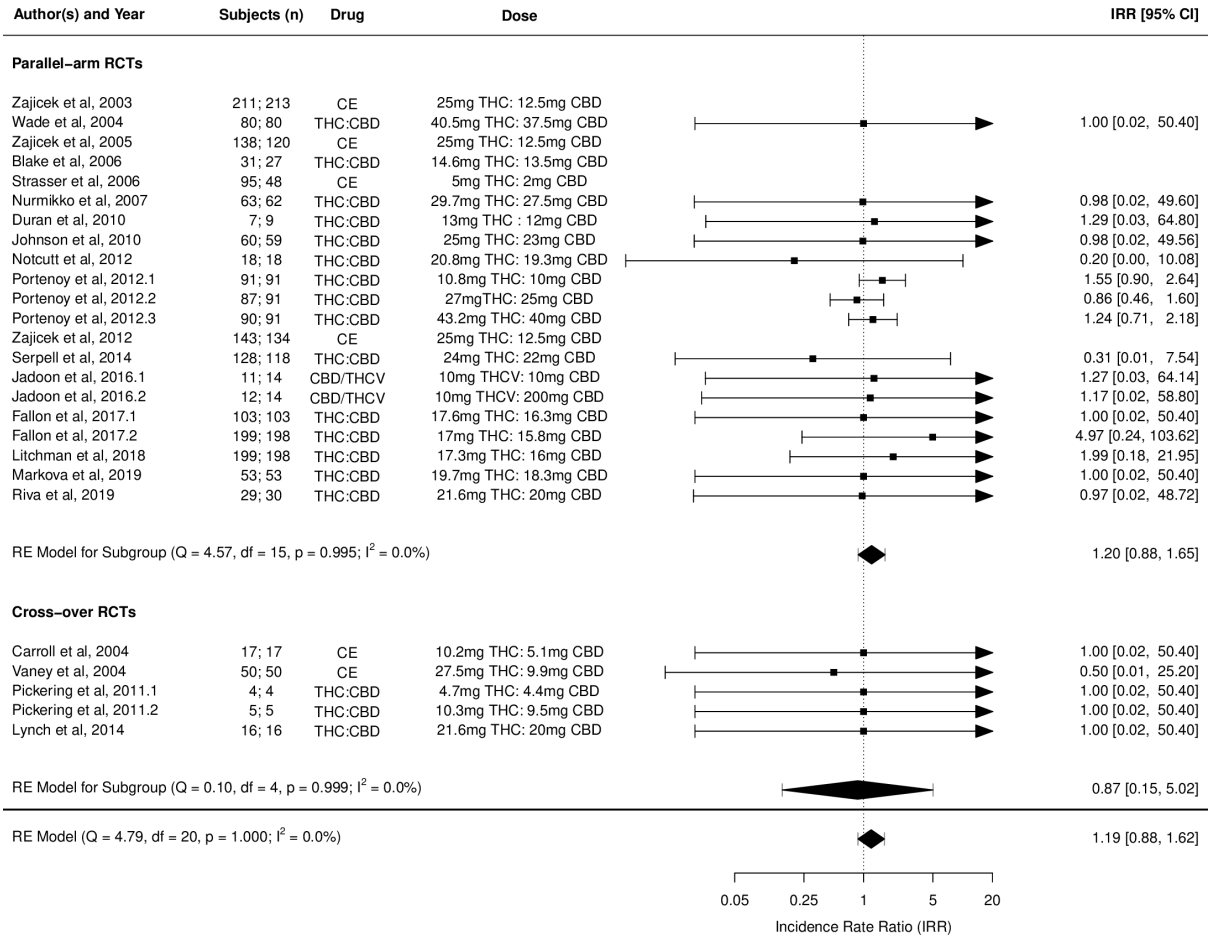
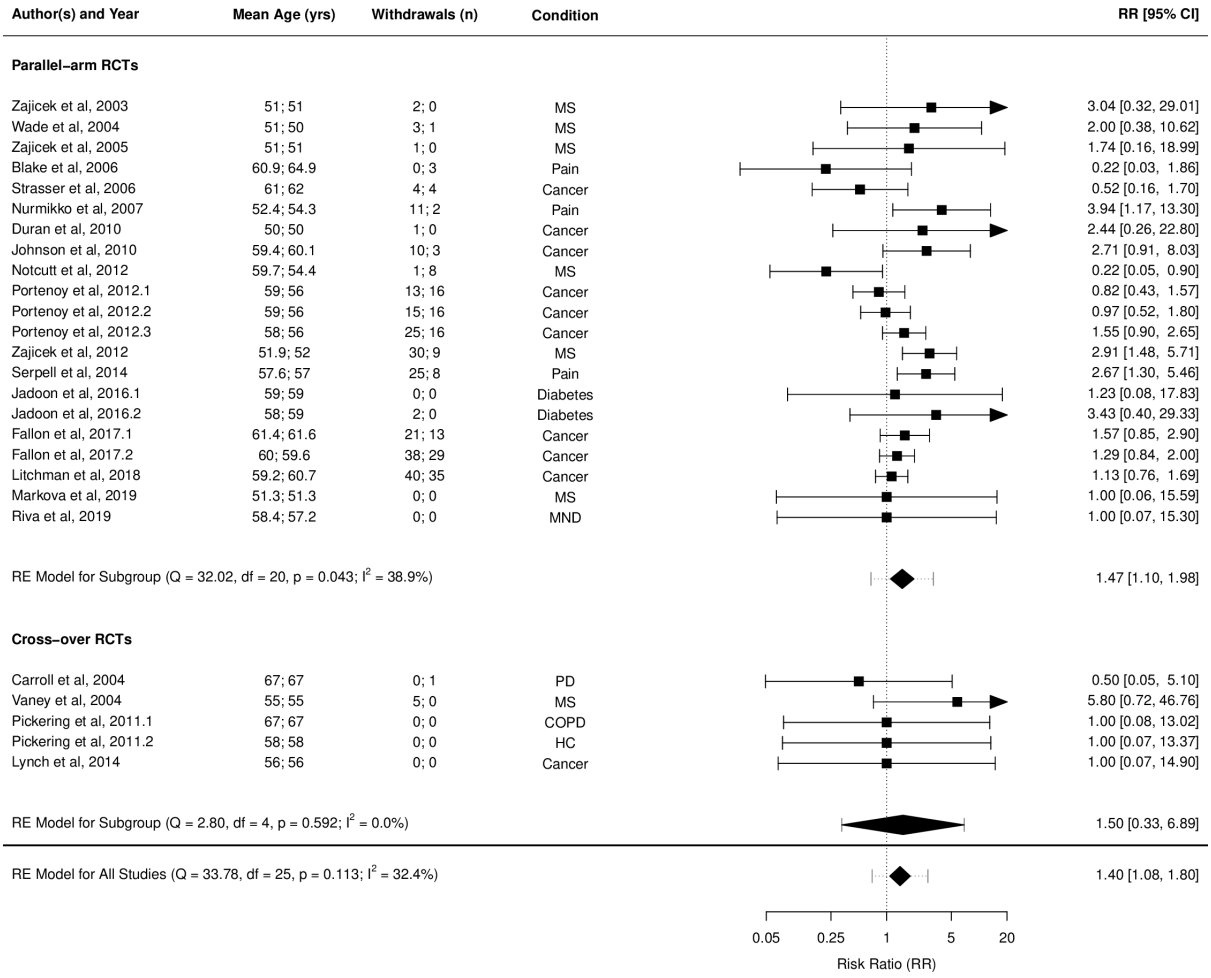


Figure 3E. Forest Plot of all Withdrawals: THC:CBD studies.

Numbers under the 'Mean Age (yrs)' and 'Withdrawals (n)' columns refer to the values in active and control intervention arms respectively.



The conditions listed are the disease conditions sub-grouped for meta-regression analyses purposes are: Multiple sclerosis (MS); motor neuron disease (MND); pain (neuropathic pain, rheumatoid arthritis), cancer (cancer or chemotherapy related anorexia, pain or nausea/vomiting), diabetes mellitus, chronic obstructive pulmonary disease (COPD), healthy controls (HC), levodopa induced dyskinesia in Parkinson's disease) (PD).

Figure 3F. Forest Plot of all deaths: THC:CBD studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively. *CE* refers to cannabis extract.

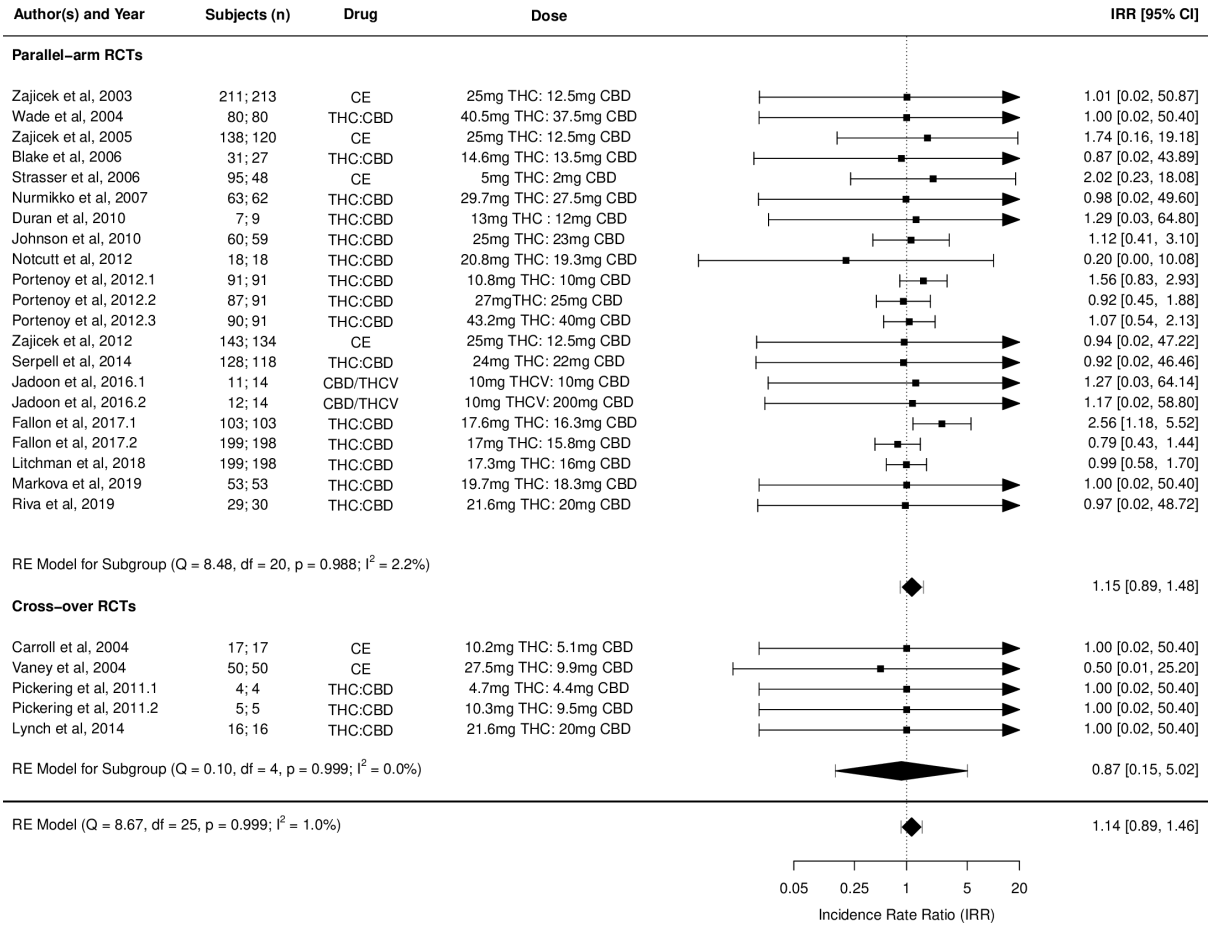
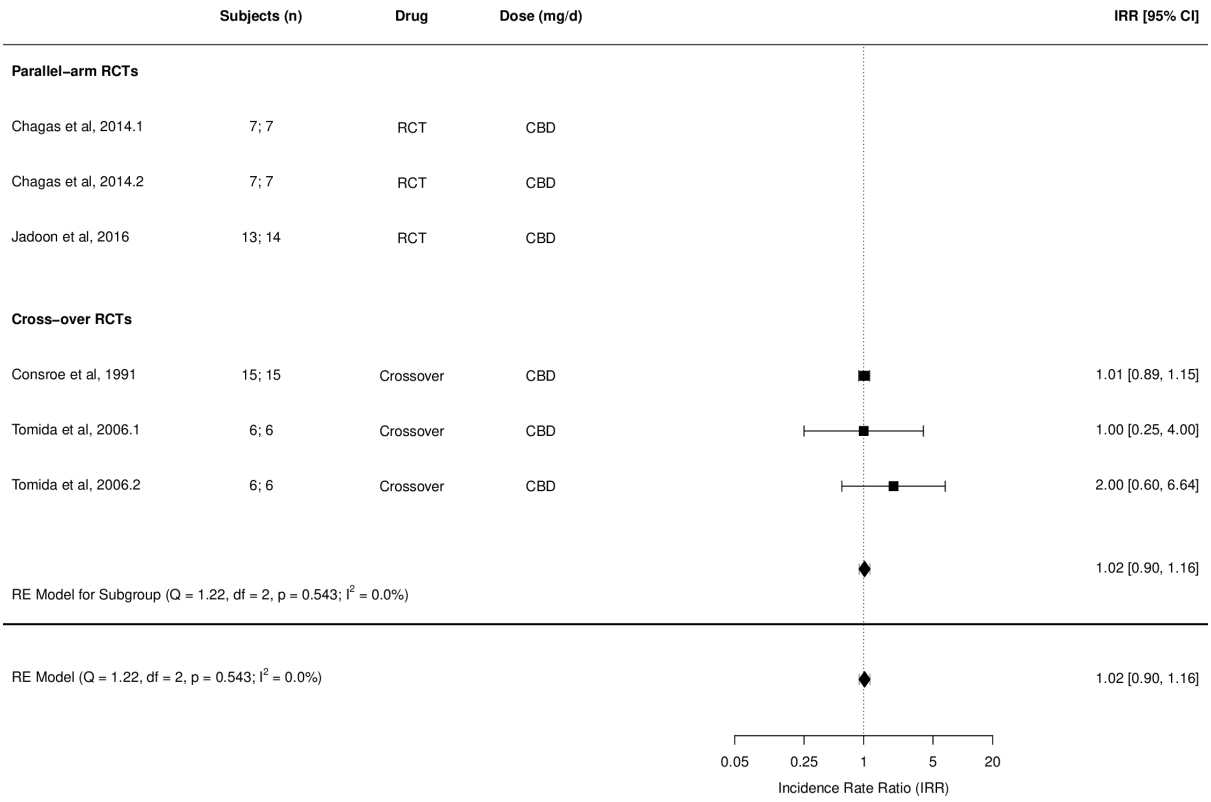


Figure 4A. Forest Plot of all cause Adverse Events: CBD studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively.



Overall study quality GRADE (Grading of Recommendations Assessment, Development and Evaluation) [31] is reported in Table 1 a-c, and Results in S2 Appendix. Risk of bias estimates are reported in Figures 2 (G, H), 3 (G, H) and Figure 4B.

Figure 2G. Risk of bias (THC studies).
Authors' judgements about each risk of bias domain for each individual study.

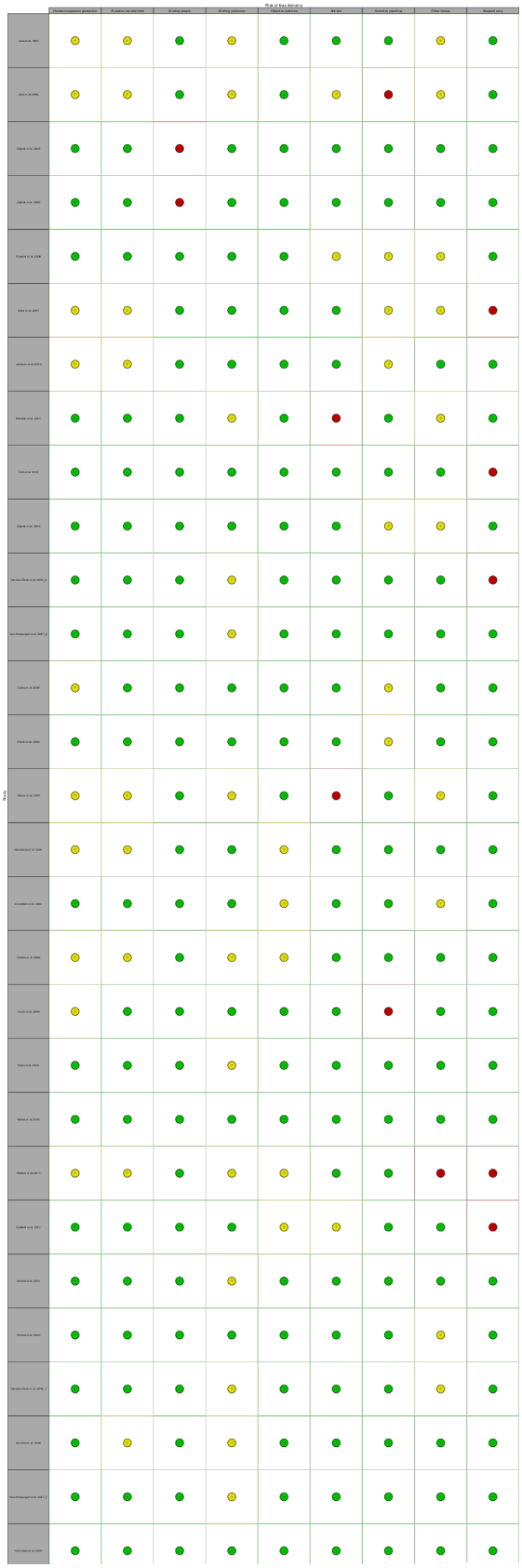


Figure 2H. Summary of risk of bias (THC studies).

Authors' judgements about each risk of bias domain reported as percentages across included studies.

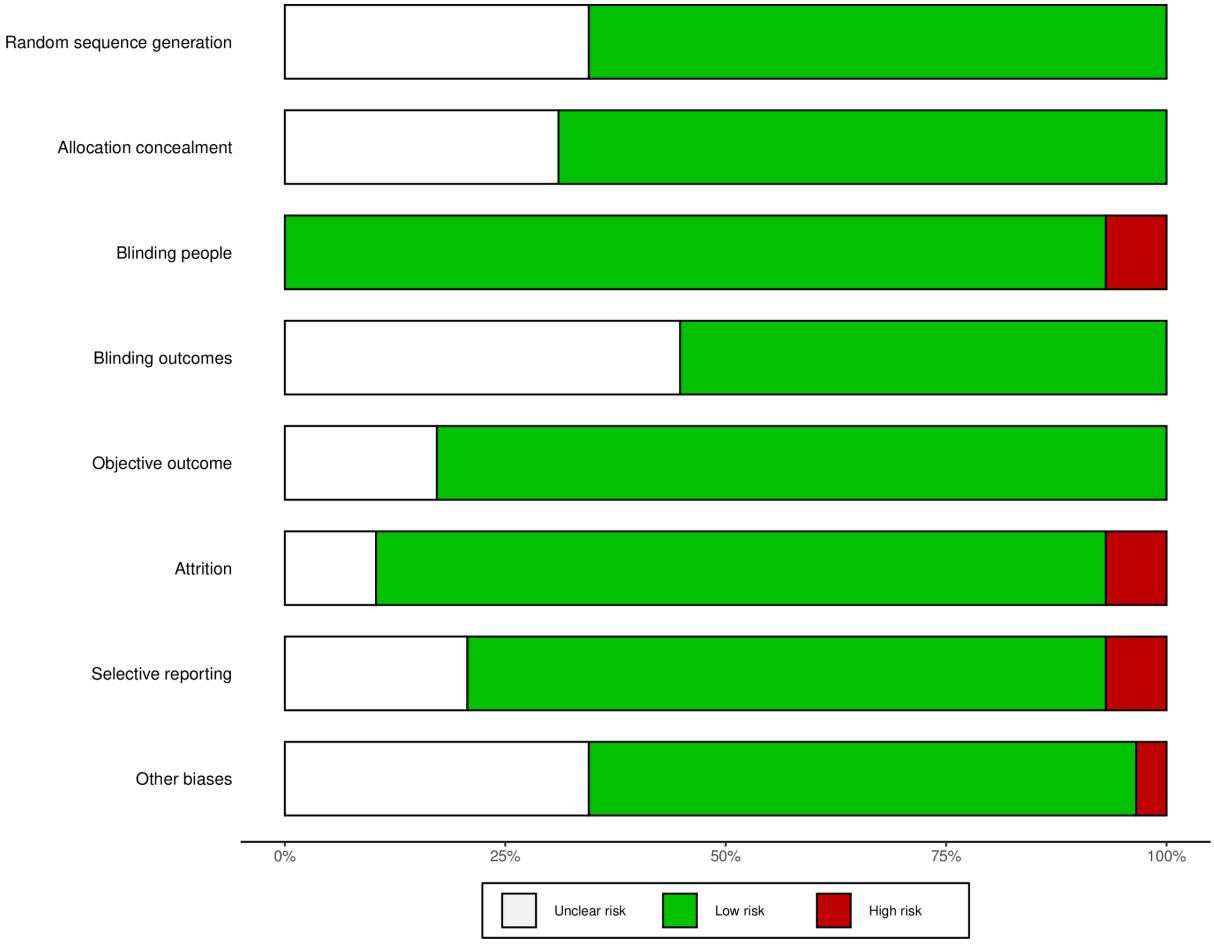


Figure 3G. Risk of bias (THC:CBD studies).

Authors' judgements about each risk of bias domain for each individual study.

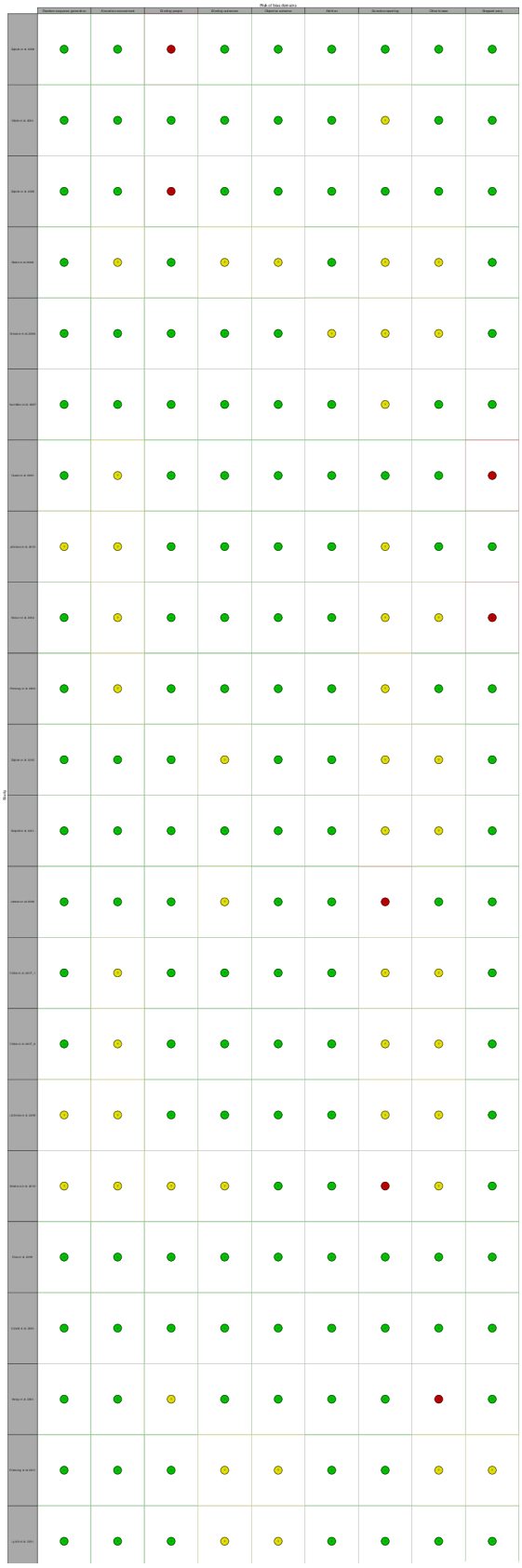


Figure 3H. Summary of risk of bias (THC:CBD studies).

Authors' judgements about each risk of bias domain reported as percentages across included studies.

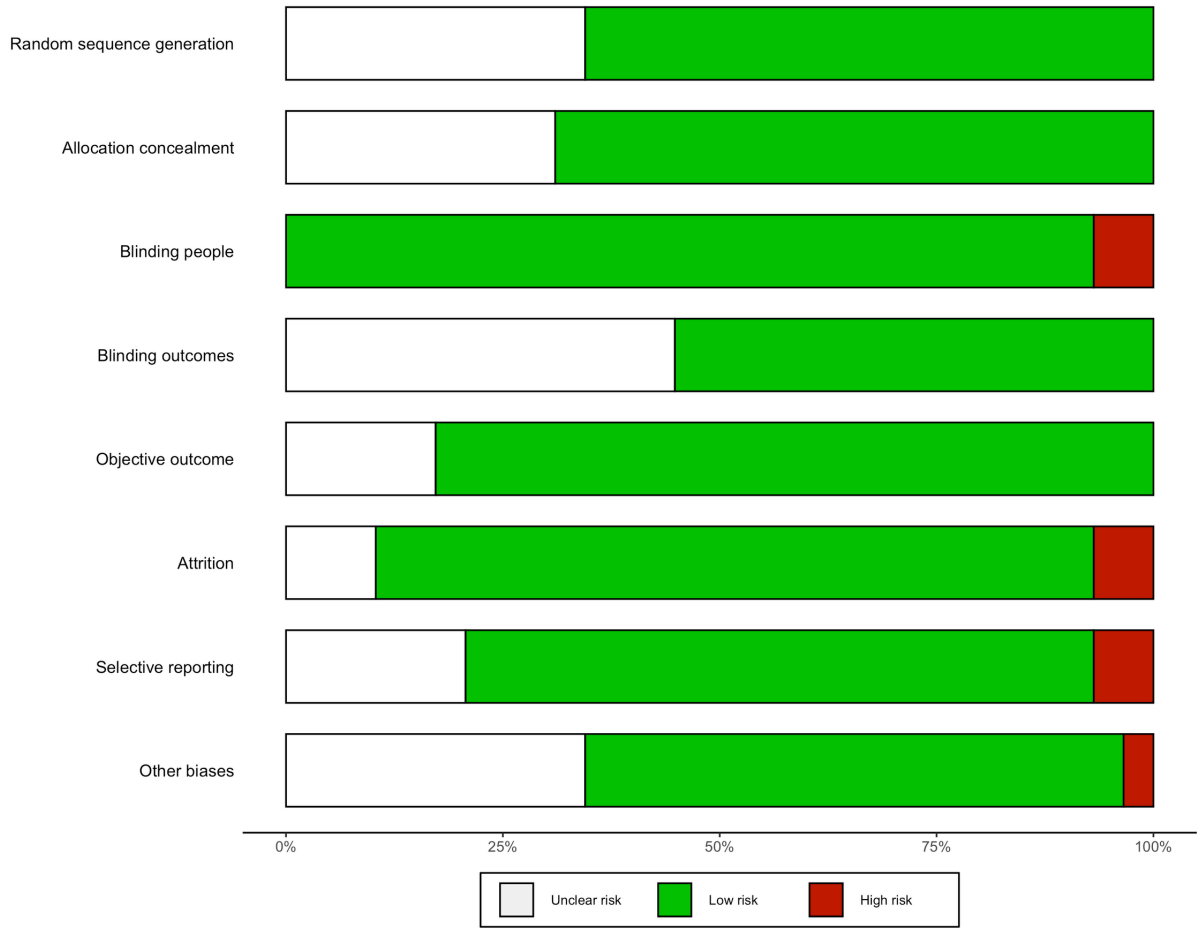
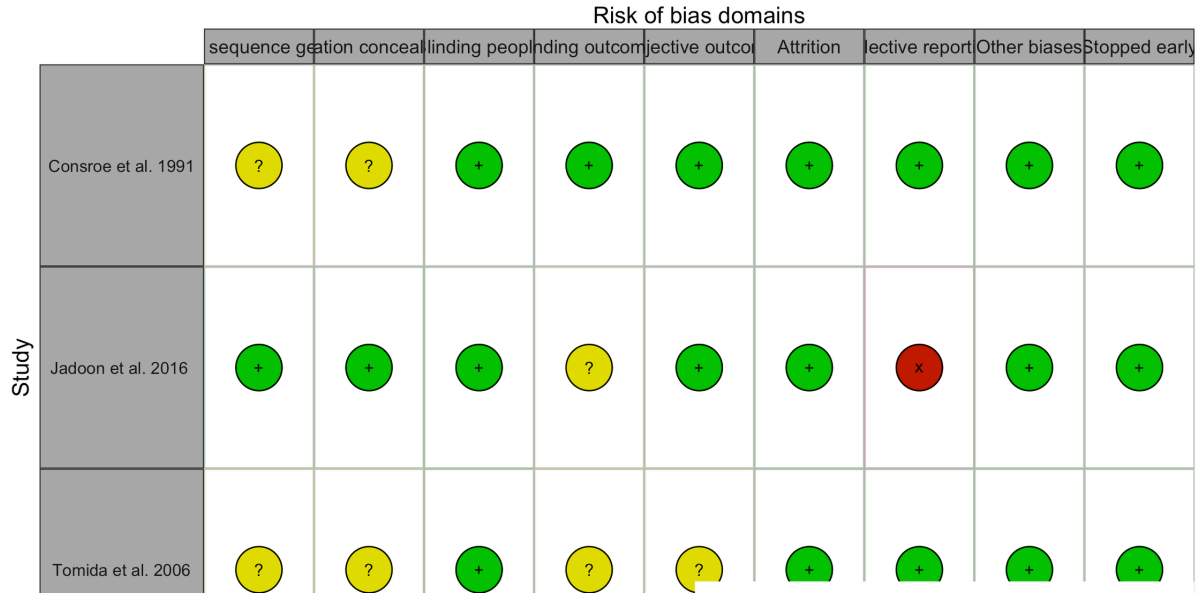


Figure 4B. Risk of bias (CBD studies).

Authors' judgements about each risk of bias domain for each individual study.



THC studies

A total of 30 RCTs (15 crossover and 15 parallel-arm) from 29 articles[39-41,43-67] (see Results in S2 Appendix and Table 2a in S2 Appendix, for additional details), reported on 1461patients on active [analysed1417; Total person-years of THC exposure: 1252.83 person-years; Mean person-years of THC exposure (mean± SD): 41.76±184.28 person-years] and 1251 (analysed 1210) patients on control intervention, ranging from 50-87 years in mean age (males: 0-100%). All except four studies used placebo control [43,45,54,62].

Pooled IRRs for all cause (*k*=21) and treatment-related AEs (*k*=9) from all RCTs were 1.42 (95% CI,1.12 -1.79) and 1.60 (95% CI, 1.26 -2.04) respectively. Pooled IRRs for all cause (*k*=27) and treatment related (*k*=23) SAEs from all RCTs were 1.08 (95% CI, 0.80 -1.46) and 1.23 (95% CI, 0.56 -2.69) respectively. Pooled RR for AE-related withdrawals (*k*=27) and IRR for all deaths (*k*=30) from all RCTs were 1.18 (95% CI,0.89 -1.57) and 1.09 (95% CI,0.75 -1.59) respectively. Neither Egger's test nor 'Trim and fill' method indicated

publication or other selection bias for any of the outcomes except for SAEs (Results in S2 Appendix and Figure 4A-F in S2 Appendix). For all cause SAEs, while Egger's test was non-significant, Trim-fill-method identified 10 missing studies. The estimated effect of treatment on IRR for all cause SAEs, which was not significant previously, became significant after inclusion of potentially missing studies identified by the trim-fill-method (1.46, 95% CI:1.09-1.95; p=0.01, *k*=35). For treatment-related SAEs, Egger's test indicated significant publication bias and Trim-fill-method identified 5 missing studies, though they did not change the direction or significance of effect-size on inclusion. Where there was non-independence of outcome data used in analyses, results of dependent meta-analyses were consistent with the results of independent meta-analyses (Results in S2 Appendix).

Effect of moderators*:*

Meta-regression analyses indicate that there was a trend-level effect [QM(df=4)=9.986, p= 0.084] of clinical condition on estimated effect of THC treatment on all cause AEs, which seemed to be mainly related to a significantly lower estimated effect in RCTs investigating neurodegenerative disorder (regression coefficient=0.905; p=0.006) patients compared to other conditions. Except that, moderators such as study design or type of intervention did not significantly influence estimated effects of THC treatment on any of the outcomes assessed.

Effect of dose:

Meta-regression analyses also indicated that there was a significant effect of daily THC dose on all cause AEs [QM (df= 1)= 5.024, p=0.025] as well as on AE-related withdrawals [QM (df= 1)= 4.696, p=0.03] for all RCTs indicating that higher the dose of THC the higher was the risk of all cause AEs and risk of withdrawal (regression coefficient = -0.905; p=0.006) from study in THC-treated patients compared to control treatment (Figure 1 in S2 Appendix). There was no significant association of daily THC dose with any of the other estimates (SAEs and deaths).

***Common side effects**:*

Pooled IRRs of the most commonly reported AEs (Table 3a in S2 Appendix) suggested significantly higher incidence rate of dry mouth, dizziness/light-headedness, mobility/balance/coordination difficulties, somnolence/drowsiness, euphoria and male impotence in active compared to control arms.

Analysis of studies where all participants were ≥50 years:

Restricting the meta-analysis to the four studies [39-41,65] that recruited participants with ≥50 years of age (total n=136; analysed n=126), results were broadly comparable to the primary analysis in the pattern of findings, though effect on all cause AEs was no longer significant. The pooled IRRs for all cause AEs (k=3) was 2.13 (95% CI, 0.46 -9.97) and treatment-related AEs (k=3) was 2.80 (95% CI, 1.09 -7.21) respectively. Pooled IRRs for all cause (k=4) and treatment related SAEs (k=2) were 1.20 (95% CI, 0.39 -3.65) and 0.50 (95% CI, 0.03 -7.99) respectively. Pooled RR for AE-related withdrawals (k=4) and IRR for all deaths (k=4) were 1.11 (95% CI, 0.49 -2.55) and 0.58 (95% CI, 0.11 -3.06) respectively (Figure 8A-F in S2 Appendix).

Analysis of studies where all participants were ≥65 years:

Restricting the meta-analysis to only the three studies [39-41] that recruited participants with ≥65 years of age (total n=58; analysed n=50), effects were also broadly comparable to the primary analysis in the pattern of findings, with the exception of effect on all cause AEs, which was no longer significant. The pooled IRRs for all cause AEs (k=3) was 2.13 (95% CI, 0.46 -9.97) and treatment-related AEs (k=2) was 2.80 (95% CI, 1.09 -7.21) respectively. Pooled IRRs for all cause (k=3) and treatment related SAEs (k=2) were 1.80 (95% CI, 0.13 -8.76) and 0.50 (95% CI, 0.03 -7.99) respectively. Pooled RR for AE-related withdrawals (k=3) and IRR for all deaths (k=3) were 1.00 (95% CI, 0.23 -4.41) and 0.42 (95% CI, 0.05 -3.42) respectively.

THC:CBD combination studies

A total of 26 studies (5 crossover and 21 were parallel-arm; see Results in S2 Appendix and Table 2b in S2 Appendix for additional details) from 21 articles [42,46,48,49,68-85] reported on 1965 patients [analysed 1940; Total person-years of THC:CBD exposure: 394.29 person-years; Mean person-years of THC exposure (mean± SD): 15.17±28.20 person-years] on active and 1887 (analysed 1863) on placebo, ranging from 50-67 years in age (males: 0-80%). All studies used placebo as control. Two of the 26 included studies [81] investigated a combination of CBD and THCV and we also examined the key effects after excluding these studies**,** which remained unchanged (please see figures 7A-F in S2 Appendix). Results of meta-analysis for individual AEs after excluding these studies was identical to the results including all studies (as shown in Table 3b in S2 Appendix) and hence not shown.

Pooled IRRs for all cause (*k*=16) and treatment-related (*k*=9) AEs from all RCTs was 1.58 (95% CI,1.26 -1.98) and 1.70 (95% CI,1.24 -2.33) respectively. Pooled IRRs for all cause (*k*=26) and treatment-related (*k*=21) SAEs from all RCTs was 1.17 (95% CI,0.99 -1.39) and 1.19 (95% CI, 0.88 -1.62) respectively. Pooled RR for AE-related withdrawals (*k*=26) and IRR for all deaths (*k*=26) from all RCTs were 1.40 (95% CI,1.08 -1.80) and 1.14 (95% CI, 0.89 -1.46) respectively. Neither Egger's test nor 'Trim and fill' method indicated any significant effect of publication or other selection bias for any of the outcomes except for deaths (Figure 5A-F in S2 Appendix). For deaths as outcome, while Egger's test was not significant, Trim and fill method indicated 9 missing studies, with the estimated effect becoming significant after their inclusion (1.33, 95% CI:1.03- 1.71; p=0.027, *k*=35). Where there was non-independence of outcome data used in analyses, results of dependent meta-analyses were consistent with the results of independent meta-analyses.

Effect of moderators:

Meta-regression analysis indicated that there was a significant effect of clinical condition on effect-size for treatment-related AEs [QM (df=3)=15.948, p= 0.01] and AE-related withdrawals [QM (df=3)=8.987, p= 0.029]. For treatment-related AEs, this was mainly related to a significantly higher effect-size in RCTs investigating pain conditions (regression coefficient = 0.393; p=0.022) and those investigating other conditions (regression coefficient = 1.263; p=002) compared to cancer conditions. For withdrawals, this was related to significantly higher effect-size in RCTs investigating pain conditions (regression coefficient = 0.816; p=0.020) and multiple sclerosis (regression coefficient = 0.675; p=0.035)compared to cancer conditions. Except these, moderators such as study design or type of intervention did not significantly influence estimated effects of THC:CBD combination treatment on any of the outcomes assessed.

Effect of dose:

There was a significant effect of daily THC dose [QM (df=1)=4.554, p= 0.033] on AE-related withdrawals (Figure 2 in S2 Appendix) and a trend-level effect on all cause [QM (df=1)=2.899, p= 0.089] and treatment-related AEs QM (df=1)=3.016, p= 0.082].. Exploratory analyses suggested that there was also a significant effect of CBD dose (QM (df=1)=4.539, p=0.033) on all cause AEs (Figure 3 in S2 Appendix) and a trend-level effect [QM (df=1)=3.145, p=0.076] on treatment-related AEs, but no significant effect on withdrawals. Effects of dose of both THC and CBD were such that the higher their dose, the higher was the effect of THC:CBD combination treatment on withdrawals and AEs (all cause and treatment-related). Except these, daily THC or CBD dose did not have any significant influence on the effects of THC:CBD combination treatment on SAEs or death.

Common side-effects:

Pooled IRRs of the most commonly reported AEs (Table 3b in S2 Appendix) suggested significantly higher incidence rate of nausea, vomiting, dry mouth, dizziness/ light-

headedness, somnolence/drowsiness, disorientation, fatigue and visual symptoms in active compared to control arms.

Analysis of studies where all participants were ≥50 years:

Restricting the meta-analysis to the 3 studies [42,68] that recruited participants with ≥50 years of age (total n= 60; analysed n=52) were similar to the primary analysis in the pattern of findings, except for treatment-related AEs and AE-related withdrawals, which were no longer significant. The pooled IRRs for all cause AEs (k=3) was 2.65 (95% CI,1.49 -4.71) and treatment-related AEs (k=2) was 4.73 (95% CI, 0.54 -41.65) respectively. Pooled IRRs for all cause (k=3) and treatment related SAEs (k=3) were 1.00 (95% CI, 0.10 -9.61) and 1.00 (95% CI, 0.10 -9.61) respectively. Pooled RR for AE-related withdrawals (k=3) and IRR for all deaths (k=3) were 0.77 (95% CI, 0.18 -3.22) and 1.00 (95% CI, 0.10 -9.61) respectively (Figure 9A-F in S2 Appendix). None of these studies reported any SAEs (either treatment-related or all cause) or death.

Analysis of studies where all participants were ≥65 years:

As analysable data was available from only one study, this analysis was not carried out.

CBD studies

Four studies (3 crossover and 1 parallel-arm RCT) from 3 articles [50,81,86] reported on 43 patients (analysed 40) on active and 44 (analysed 41) on placebo, with age ranging from 53-59 years [53-100% males; person-years of total CBD exposure: 6.60 person-years; Mean person-years of CBD exposure (mean± SD: 1.10±1.23 person-years)]. Pooled IRR for all cause AEs for all RCTs was 1.02 (95% CI,0.90 -1.16), based on data available only from the 2 crossover studies reporting on 3 different dosage conditions (Figure 3A and Figure 6 in S2 Appendix). There was limited data to allow quantitative synthesis of other outcomes, however, there were no treatment-related SAEs, withdrawals or death reported (see

Supplement Results, for qualitative synthesis). No analysable data was available from studies where all study participants were ≥50 years age.

Risk of bias:

A summary of the risk of bias of included studies are presented in the figures 2 (G,H), figures 3 (G,H) and Figure 4B. Briefly, most RCTs reported adequate randomisation sequence generation and concealment, outcome objectiveness and masking of outcome assessors; however some studies had high risk of bias because of potential for unmasking of participants and study personnel and selective reporting of the safety outcome. Most studies reported objective outcome assessments, however only 60% of studies reported that outcome assessors had been appropriately blinded. 45% studies did selective reporting i.e., they did not report data for all the safety outcomes (AEs and SAEs) in the trial and reported them when they occurred more than once or were more common or when they had occurrence above a certain threshold (1%-10%). The authors judged 33 (55%) trials at low risk of bias, 20 (33%) trials at unclear risk of bias and seven (12%) trials to have high risk of bias for safety outcome reporting (figures 2 G-H, figure 3 G-H and figure 4B). Overall, 36 trials were judged to be of moderate quality, of which 15 (42%) trials reported all AEs and SAEs. 10 (56%) of moderate-quality trials of THC only intervention reported all AEs and SAEs.

DISCUSSION

In this systematic review and meta-analysis, we investigated the safety and tolerability of medicinal cannabinoids in older adults by pooling data from double-blind RCTs with a reported mean participant age of 50 years and over. We hypothesized that compared to control treatments all 3 categories of CBMs will be associated with a greater incidence of AEs, but no greater incidence of SAEs, death or risk of withdrawal from study. We also expected a direct relationship between the dose of THC used in THC-containing CBMs and the risk of adverse outcomes. We found that generally moderate to high quality evidence

(about 60% studies) suggests that as hypothesized, treatment with THC-containing medications (THC alone and THC:CBD combination) was associated on average with significantly higher incidence of all-cause and treatment-related AEs compared to control treatments. Further, consistent with our hypotheses, the average incidence rates of serious AEs (all-cause and treatment-related) and death were not significantly greater under CBMs compared to controls in studies using THC with or without CBD. However, contrary to expectation, significantly higher risk of withdrawal related to AEs was noted on average for studies using THC:CBD combination, though this was not observed in studies that used THC without CBD. In contrast, generally low-quality evidence (about 67% of studies) suggests that CBD alone may not significantly increase the incidence rate of all-cause of AEs. Qualitative synthesis of data on treatment-related AEs, SAEs, deaths and withdrawals from study also did not suggest any increase associated with CBMs containing CBD alone. In terms of relationship between THC dose and adverse outcomes, as hypothesized, we found a direct relationship between daily THC dose and all cause AEs and AE-related withdrawals in THC studies and between THC dose and AE-related withdrawals in THC:CBD studies. Contrary to our expectations, we did not find any association between THC dose and the other outcomes investigated, such as SAEs and deaths. In addition, exploratory analysis showed that CBD dose also had a significant direct relationship with all-case AEs and a strong trend-level association with treatment-related AEs in RCTs using THC-CBD combination.

Additional analyses restricted to only those studies in which all participants were ≥50 years of age or ≥ 65 years of age, where this was feasible, indicated a pattern of findings broadly comparable with the results of our main analyses including all studies. However, the effect of CBMs containing THC but no CBD on all cause AEs and CBMs containing THC:CBD on treatment-related AEs and AE-related withdrawals were no longer significant, which likely reflects the lower power of these analyses which included a maximum of 4 studies in any analysis.

Collectively, our results from studies that included participants with a mean age ≥ 50 years may suggest that older adults are at significantly greater risk of both treatment-related and all cause AEs from CBMs containing THC, but not using CBMs without THC. Despite the greater risk of AEs, older adults receiving CBMs do not seem to be at a significantly greater risk of more serious consequences such as SAEs or death. Greater risk of withdrawal from study in those receiving CBMs containing THC:CBD combination but not in those containing THC or CBD without the other cannabinoid is an unexpected finding. While we did not compare these two effects in a systematic manner, if true, this may suggest that combination of these cannabinoids may be less acceptable in this age group, who already may be receiving multiple treatments for comorbidities. What may underlie these effects is much less clear. One may speculate that this may be a result of the generally higher THC dose employed in THC:CBD studies compared to the THC studies, which may have made participants in the former group of studies more susceptible to AEs and withdrawal as a result compared to those receiving THC. This is supported by approximately double the median dose of THC used in THC:CBD studies [median and interquartile range: 10.3(10.2-21.6) mg/ day in crossover and 20.8(14.6-25) mg/ day in parallel-arm RCTs] as opposed to THC studies [median and interquartile range: 5(2.25-9 mg/ day in crossover and 10(4.8-25) mg/ day in parallel-arm RCTs]. In accordance with this hypothesis, there was a nominally higher incidence of AEs in general in those studies using both cannabinoids in combination compared to THC studies. However, one cannot completely rule out the possibility that greater risk of withdrawal from study in those receiving CBMs containing THC:CBD combination but not in those containing THC or CBD without the other cannabinoid, as observed here, is purely by chance. Further, THC dose was significantly associated with withdrawal in both study groups using THC-containing medications. In contrast, CBD dose was only associated with AEs but not withdrawal in those using THC:CBD combination. However, whether these results suggest that lower acceptability of THC:CBD combination is a tolerability issue in older patients because of combination of cannabinoids rather than

being related to the dose of CBD, remains to be formally tested. It is also worth noting that the evidence base of studies that used CBMs without THC in older adults and found it to be well-tolerated is relatively sparse. Whether this may underlie the absence of significantly greater risk of all cause AEs as a result of treatment with CBMs without THC compared to controls, contrary to our expectation, remains to be tested. However, more generally, lack of significant AEs associated with CBD treatment alone in the present study is consistent with other analyses suggesting a good tolerability profile of CBD alone in younger age groups [87,88]. Nevertheless, collectively these results suggest that although the incidence of side-effects is greater with THC-containing products, CBMs investigated in these studies are generally safe. Their overall tolerability profile also seems to be generally acceptable to patients, though combination of THC and CBD may be less so. It is important to note that although the general pattern of results of analyses restricted to studies where all participants were ≥50 years of age or ≥ 65 years of age were broadly comparable with results from our main analyses of studies with mean participant age ≥50 years, they were not identical, indicating that effects of CBMs may be different when focused exclusively on adults over 65 or 75 years of age.

Although we did observe a significant association between THC dose and all cause AEs in THC studies, this was not present in THC:CBD studies. Whether this reflects independent evidence that CBD may mitigate some of the adverse effects of THC, such as on cognition, behaviour, autonomic and cardiovascular function [15,25-28] and therefore may have obscured any dose-response relationship with AEs in THC:CBD studies remains unclear. The present study was not designed to formally test this hypothesis, which needs independent examination.

Finally, we identified a number of specific AEs associated with CBMs containing THC:CBD combination or THC without CBD. Of the specific AEs, significantly increased incidence of

dizziness/ light headedness, drowsiness, disorientation and impaired mobility/ balance/coordination is worth noting, in light of higher risk of falls in this age group, which may be further exacerbated by these treatments [89,90].

Pooled estimates of all cause AEs under both THC and THC:CBD and of treatment-related AEs and AE-related withdrawals under THC:CBD as reported herein need to be considered carefully in light of high-levels of heterogeneity (discussed further below) in the studies as evident from the estimated I^2 statistic (>32% in all these estimates). Therefore, we have also reported the prediction intervals along with the 95% confidence intervals in the forest plots for the key pooled estimates reported herein. These prediction intervals indicate that while the average effects of CBM treatments on these outcomes are significant (as evident from the 95% confidence intervals), the range of predicted effects across different study settings that may be observed in a new study may span a wider range of effect sizes than indicated by the 95% confidence intervals. Some of these predicted effect-sizes in new studies are likely to be <1 indicating that the risk of these outcomes with THC or THC:CBD treatment may not be higher than under control treatment condition.

Previous reviews of adverse consequences of treatment with CBMs have either been qualitative [12,19,20], did not specifically focus on older adults [16,17] or did not consider the effects of THC, CBD or their combination separately [12,16,17]. Even in studies that have pooled the adverse event data quantitatively, this has been done based on specific formulation rather than on the basis of their cannabinoid content [16,17]. Further, they have generally reported summary effect-size estimates (such as odds ratio) that do not take into account person-years of treatment, an important consideration in quantitative synthesis of outcomes from RCTs [16,17]. As in previous reviews, we found that not all studies have published all the AEs and SAEs and that there is lack of evidence of the safety, tolerability and acceptability specifically in older patients. Nevertheless, our findings are consistent with previous reviews which found dizziness to be the most common non-serious AE with CBM

treatment [12,16,17]. These results are also consistent with a prospective observational study of 901 people above 65 years of age (74.5 ± 7.5 years), who received medical cannabis from January 2015 to October 2017 in a specialized medical cannabis clinic, 31.7% reported at least one AE due to the treatment after six months, with dizziness (9.7%) and dry mouth (7.1%) as the commonest AEs [21]. Another similar study of 184 people (81.2 ± 7.5 years of age) from April 2017 to October 2018 showed 33.6% with AEs and dizziness (12.1%) and sleepiness and fatigue (11.2%) as the commonest AEs [91]. A previous systematic review of the efficacy and safety of medicinal cannabinoids which focused only on older people considered 5 controlled trials with THC (n = 3) and oral THC:CBD (n = 2) [12]. However, this review did not provide summary estimates (effect sizes) due to high heterogeneity among the included studies, lack of available data on means and standard deviations per treatment group, and very small sample sizes [12]. Therefore, only qualitative and descriptive summaries were provided. Studies included in this review reported dizziness, euphoria, drowsiness, confusion, and disorientation as the common adverse effects [12], consistent with our report. An earlier systematic review of AEs of medicinal cannabinoids for all ages by Wang et al [17] included 23 RCTs published between 1966 and late 2007, and analysed the effect of oral THC, and THC:CBD oral and spray formulations. However, they did not include data from studies examining the synthetic cannabinoid nabilone and found no evidence of higher incidence of SAEs after a median of 2 weeks use compared with a control group, regardless of the age of individuals (RR 1.04, 95% CI 0.78 - 1.30). Wang and colleagues [17] reported that respiratory, gastrointestinal and nervous system disorders were the most frequently reported categories of SAEs and dizziness was the most commonly reported nonserious AE (15.5%) among people exposed to cannabinoids. However, unlike the present review wherein we have used GRADE criteria to assess methodological quality of included RCTs, Wang et al used a scale reported in a manuscript by Jadad and colleagues [92] to assess methodological quality of RCTs. As the scale from Jadad and colleagues does not adequately assess the quality of safety reporting

in RCTs, most studies were rated as of good quality in the review by Wang et al, despite their poor reporting of safety [17].

However, our results are not consistent with a more recent systematic review and meta-analysis by Whiting et al [16], which included studies investigating all age groups and showed that SAEs and AE-related withdrawal are generally higher in those treated with CBMs. In contrast, we have shown that SAEs are not increased in older adults consistent with other reviews [12,17]. Whiting et al [16] found pooled effect-size for any AE (OR 3.03,95% CI 2.42-3.80), SAE (OR 1.41, 95% CI 1.04-1.92) and withdrawal due to AE (OR 2.94, 95% CI 2.18-3.96) and Wang et al [17] found significantly higher non-serious AEs (RR 1.86, 95% CI 1.57-2.21) in those who received CBMs compared to control groups. In contrast to Whiting et al, we have shown that increase in withdrawal may be more nuanced and more in those receiving THC:CBD combination and not for other types of CBMs.

It is difficult to compare our pooled effect-size with previous reviews due to a number of reasons. Firstly, Whiting reported odds ratios and Wang et al reported relative risk, wherein we have reported IRR. In the present context, the risk of AEs or SAEs in either study arm are unlikely to be constant over time. Therefore, IRR which takes into consideration person-years of treatment and is a ratio of the incidence rate in the experimental treatment group to that in the control treatment group, is more meaningful and appropriate in contrast to the odds ratio, which is a ratio of the odds of an event in the experimental group to that in the control group and are not easily interpretable. Secondly, we carried out a pooled analysis for individual interventions unlike the other reviews, with Wang et al also excluding studies using Nabilone [17]. Finally, the 2 previous reviews that reported summary estimates included all age groups and were not specific for older people unlike here.

Our results extend previous literature by showing that although at significantly higher risk of adverse events from CBMs containing THC, but not from those without THC, CBMs are

generally safe in older adults, who typically experience co-morbid health conditions[93] and receive polypharmacy [94]. Also, CBMs are generally acceptable as long as they are not a combination of THC and CBD.

Results presented here may also need to be considered against the side-effect profile of common treatments for the clinical conditions investigated in studies included in the meta-analyses reported here, as safety and tolerability profile of a potential new treatment relative to existing alternatives is an important consideration in the context of prescribing. Studies included patients with Alzheimer's disease, Parkinson's disease, Huntington's disease. Amyotrophic lateral sclerosis, multiple sclerosis, motor neuron disease, neuropathic pain, cancer (cancer or chemotherapy related anorexia, pain or nausea/vomiting), type 2 diabetes mellitus, chronic obstructive pulmonary disease, fibromyalgia, raised intraocular pressure, cervical dystonia, pancreatitis and obstructive sleep apnoea. As would be expected, these conditions are typically treated with a wide range of pharmacological treatments (opioid analgesics, non-steroidal anti-inflammatory, anti-epileptics, benzodiazepines, psychotropics, cholinesterase inhibitors, glutamate antagonists, dopamine agonists, immunosuppressants, muscle relaxants, etc) with a varied side-effect profile. While a systematic comparison of side-effect profile of CBMs and these other treatments would be useful and can helpfully inform prescribing decisions, this was outside the scope of the present review and was not examined here. Therefore, future studies may need to investigate this in a systematic manner. As we pooled data from randomized controlled comparisons, as opposed to observational studies without a control arm, they are very unlikely to have confounded the results presented herein.

Strengths and limitations

Our review and meta-analysis are limited by a number of methodological weaknesses some of which stem from the design and analytic approach of the present study and others which

are related to weaknesses in the studies that were included in the present analysis. One of the key limitations inherent in the meta-analytic approach that also applies to the present study relates to the issue of heterogeneity in the pooled data [95]. Studies pooled in our analyses focused on patients with different clinical conditions and indications, used different doses, formulations and routes of administration of the study drug for different treatment periods and employed different study designs (cross-over versus parallel-arm RCTs). Further, although we attempted to control for patients from widely disparate age groups taking part in the trial by setting an inclusion criterion of mean age of 50 years and over as the cut-off, studies included in our main analyses still involved data from people below age 50 and studies also varied in terms of sex distribution. This is reflected in the heterogeneity estimates reported in our results. In order to address this wide-ranging heterogeneity and yet pool the data in a meaningful way, we employed a random-effects model in our analyses, which assumes that there will be variability in the observed estimates of treatment effects across studies, both as a result of real differences in the effect of treatment between studies as well as by chance because of sampling variability. As a result, pooled estimates reported are not precise (as may be evident from the wide confidence intervals) and should not be considered as such. Effects reported here represent an average effect of CBM treatments on safety and tolerability outcomes investigated rather than an effect that is common across studies. As the effects may be different within an individual study, we also report a prediction interval for our key reported outcomes, in order to give an estimate of the range of predicted effects across study settings that may be observed in a new study. Further, we also carried out sub-group (e.g. cross-over and parallel-arm RCTs separately) and meta-regression analyses to examine the sources of heterogeneity for THC and THC:CBD studies. These analyses did not suggest that study design or type of intervention had any significant effect on the outcomes assessed, though they suggest that effects vary, sometimes significantly, across clinical conditions investigated in the RCTs. They were more pronounced in AE-related withdrawals and treatment-related AEs in THC:CBD studies and less so for all cause AEs in studies investigating THC as a treatment. Dose of study drug also seemed to underlie

some of the heterogeneity observed in all cause and treatment-related AEs and AE-related withdrawals in the THC and THC:CBD studies. Another limitation relates to the fact that we were not able to systematically examine the sources of heterogeneity for CBD alone studies as there were fewer studies than recommended for such analyses. One other limitation of the present meta-analysis relates to our focus on studies reporting on participants aged 50 years and over.

Further, we included studies in which the mean age of study participants was ≥50 years (although the studies also included many participants who were <50 years of age). As the cut-off employed by us differs from the conventional threshold of 65 years for 'elderly' [96], this may be considered as a limitation. However, this was chosen as the clinical conditions (diabetes, cancer, neurodegenerative disorders, cancer etc) for which CBMs are often considered become more common from around this age. This is also a period characterised by multi-morbidities, polypharmacy and age-related bodily changes that may affect pharmacokinetics [96] and tolerability of medications. Further, in order to address the limitation that many participants in the included studies were <50 years of age, we also carried out sensitivity analysis that included studies where all participants were ≥ 50 years of age. The results of these analyses suggest that the pooled effect-sizes were generally in the same direction as that reported from the larger set of studies, though the confidence intervals were wider, as may be expected. We have also reported the number of studies which have actually studied individuals with age ≥ 65 years or ≥ 75 years. As evident from this, there is a very limited set of studies that have exclusively focused on people at these ages. Therefore, the present meta-analysis highlights the need for studies that may need to focus on people over 65. However, given the age range as well as median and interquartile range of the mean ages of study participants included in the studies that constitute our meta-analysis, it is clear that people over 65 and 75 years are currently being recruited into studies of CBMs for various indications. As individual RCTs are often not powerful enough to

unravel patterns of side-effects and given the growing use of CBMs in the elderly and general perception of them being safe, it is particularly important to summarize currently available evidence to help inform about the safety and tolerability profile of CBMs in those aged 50 years and over rather than wait for the evidence base focusing only on ≥ 65 years to mature. In the fullness of time, future attempts at evidence synthesis need to focus only on studies of people ≥ 65 years when a sufficient number of studies have accumulated.

The other main source of limitation stems from methodological limitations in the included trials as identified during quality assessment [30,31], specifically pertaining to selective outcome reporting, and inadequate description of methods of randomization, allocation concealment, and blinding. Additionally, many included RCTs investigated only modestly sized samples [41,42,44,50,57]. Small samples render studies particularly underpowered when estimating serious and less serious adverse outcomes, which by their nature may not occur frequently. It is in this context, that the present report addresses an important gap in extant evidence by systematic quantitative synthesis of RCT data following existing recommendations [30,31] to provide estimates from a larger pool of patients. Further, our analyses suggest that publication or other selection biases are unlikely to have influenced the pooled estimates reported here.

Unlike in previous meta-analyses, which reported summary effects separately based on indications, we pooled safety and tolerability data in older adults across a broad range of indications. While this may have added to the heterogeneity of the data synthesized, it allowed us to comprehensively estimate separately the effects of three broad categories of cannabinoid-based interventions i.e., THC only, THC:CBD combination and CBD only, something that has not been done before. This is a key strength of the present approach, given the reported opposite effects of different cannabinoids [4,15] that argue against data being combined. Another important strength of the present report relates to the analysis of

the effects of moderators to examine the extent to which they may have influenced results, in particular relationship with cannabinoid doses used.

Studies evaluated various routes of CBM administration (oral capsules, tablets, sublingual spray, oromucosal spray). Also, not all studies compared CBMs with placebo, with four studies using active control treatments [43,45,54,62]. While all of these may have resulted in a very heterogeneous set of included studies, we used a random-effects model to mitigate these effects. Further, heterogeneity did not seem to significantly affect any of our estimates other than all cause AEs, giving further confidence in the results reported. Nevertheless, we have also reported prediction intervals in addition for our key reported outcomes to give an estimate of the range of predicted effects across different study settings. Finally, another important potential limitation of the present study relates to the fact that we did not investigate the efficacy of CBMs in older adults. As outcome measures used to index efficacy vary widely between clinical conditions and there is a relative paucity of studies investigating a particular clinical condition, there is not enough data for any quantitative synthesis of efficacy of different CBMs in older adults to be meaningful just yet.

Clinical efficacy is one of the foremost considerations in addition to patient choice and safety / tolerability of interventions when prescribing in clinical practice. While the present study summarizes current evidence regarding safety / tolerability of CBMS, there is limited efficacy evidence for most clinical indications for which CBMS have been used in older people. Therefore, there is a pressing need for efficacy studies in specific indications where there is proof of concept or rationale for use of CBMs in older people. With regard to CBMs, potential for drug-drug interaction in light of effect on cytochrome p450 enzymes is a major concern in the context of treating older patients [13]. However, few studies have examined this, an important likely determinant of tolerability and dose adjustment, and therefore worthy of investigation in future studies.

Complete reporting of safety/ tolerability data as well as improved trial designs incorporating robust methods for allocation concealment, masking of participant and outcome assessors are further important considerations for future trials. Using well-powered samples, such studies need to focus on safety, tolerability as well as efficacy of different categories of CBMs, in particular CBD on its own, a relatively less investigated CBM in older people.

Conclusion

Results of the present study using data from RCTs with mean participant age ≥ 50 years suggest that although THC-containing CBMs are associated with side-effects in those aged 50 years and over, in general CBMs are safe and acceptable treatments in older adults, with a caveat that THC:CBD combinations may be less so at least in dose ranges used in studies thus far. However, tolerability may be different in adults over 65 or 75 years of age, and robust evidence of efficacy of different CBMs for specific indications is needed before they may be used in routine practice in older adults.

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Supporting Information (S2 Appendix) Captions:

Figure 1. THC dose related withdrawals in THC studies

Figure 2. THC dose related withdrawals in THC:CBD studies

Figure 3. CBD dose related all cause AEs in THC:CBD studies

Figure 4: Funnel plots for all tolerability and safety outcomes: THC studies

a. All cause Adverse Events (AEs); b. Treatment-related AEs; c. All cause Serious Adverse Events (AAEs); d. Treatment-related SAEs; e. AE-related Withdrawals; f. Deaths.

Figure 5: Funnel plots for all tolerability and safety outcomes: THC:CBD studies

a. All cause Adverse Events (AEs); b. Treatment-related AEs; c. All cause Serious Adverse Events (AAEs); d. Treatment-related SAEs; e. AE-related Withdrawals; f. Deaths.

Figure 6: Funnel plot for all cause Adverse Events (AEs): CBD studies

Figure 7A. Forest Plot of all cause Adverse Events: THC:CBD studies (excluding THCV).

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively. *CE* refers to cannabis extract.

Figure 7B. Forest Plot of treatment-related Adverse Events: THC:CBD studies (excluding THCV).

Numbers under the ‘Subjects (n)’ column refer to analysed subjects from the active and control intervention arms respectively. *CE* refers to cannabis extract.

Figure 7C. Forest Plot of all cause Serious Adverse Events: THC:CBD studies. (excluding THCV).

Numbers under the ‘Subjects (n)’ column refer to analysed subjects from the active and control intervention arms respectively. *CE* refers to cannabis extract.

Figure 7D. Forest Plot of treatment-related Serious Adverse Events: THC:CBD studies (excluding THCV).

Numbers under the ‘Subjects (n)’ column refer to analysed subjects from the active and control intervention arms respectively. *CE* refers to cannabis extract.

Figure 7E. Forest Plot of all Withdrawals: THC:CBD studies (excluding THCV).

Numbers under the ‘Mean Age (yrs)’ and ‘Withdrawals (n)’ columns refer to the values in active and control intervention arms respectively.

The conditions listed are the disease conditions sub-grouped for meta-regression analyses purposes are: Multiple sclerosis (MS); motor neuron disease (MND); pain (neuropathic pain, rheumatoid arthritis), cancer (cancer or chemotherapy related anorexia, pain or nausea/vomiting), diabetes mellitus, chronic obstructive pulmonary disease (COPD), healthy controls (HC), levodopa induced dyskinesia in Parkinson’s disease) (PD).

Figure 7F. Forest Plot of all deaths: THC:CBD studies (excluding THCV).

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively. *CE* refers to cannabis extract.

Figure 8A. Forest Plot of all cause Adverse Events: THC studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively.

Figure 8B. Forest Plot of treatment-related Serious Adverse Events: THC studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively.

Figure 8C. Forest Plot of all cause Serious Adverse Events: THC studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively.

Figure 8D. Forest Plot of treatment-related Serious Adverse Events: THC studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively.

Figure 8E. Forest Plot of Adverse Event-related Withdrawals: THC studies.

Numbers under the 'Mean Age (yrs)' and 'Withdrawals (n)' columns refer to the values in active and control intervention arms respectively.

The conditions listed are the disease conditions sub-grouped into broader categories for meta-regression analyses purposes. They are: Neurodegenerative disorders (ND) (dementia, Alzheimer's disease, Parkinson's disease (PD), Huntington's disease, Amyotrophic lateral sclerosis); Multiple sclerosis (MS); Cancer (cancer or chemotherapy related anorexia, pain or nausea/vomiting, chemosensory alterations); and Other (type 2 diabetes mellitus, fibromyalgia, raised intraocular pressure, cervical dystonia, healthy, pancreatitis, obstructive sleep apnoea).

Figure 8F. Forest Plot of all deaths: THC studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively.

Figure 9A. Forest Plot of all cause Adverse Events: THC:CBD studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively. *CE* refers to cannabis extract.

Figure 9B. Forest Plot of treatment-related Adverse Events: THC:CBD studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively. *CE* refers to cannabis extract.

Figure 9C. Forest Plot of all cause Serious Adverse Events: THC:CBD studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively. *CE* refers to cannabis extract.

Figure 9D. Forest Plot of treatment-related Serious Adverse Events: THC:CBD studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively. *CE* refers to cannabis extract.

Figure 9E. Forest Plot of all Withdrawals: THC:CBD studies.

Numbers under the 'Mean Age (yrs)' and 'Withdrawals (n)' columns refer to the values in active and control intervention arms respectively.

The conditions listed are the disease conditions sub-grouped for meta-regression analyses purposes are: Multiple sclerosis (MS); motor neuron disease (MND); pain (neuropathic pain, rheumatoid arthritis), cancer (cancer or chemotherapy related anorexia, pain or nausea/vomiting), diabetes mellitus, chronic obstructive pulmonary disease (COPD), healthy controls (HC), levodopa induced dyskinesia in Parkinson's disease) (PD).

Figure 9F. Forest Plot of all deaths: THC:CBD studies.

Numbers under the 'Subjects (n)' column refer to analysed subjects from the active and control intervention arms respectively. *CE* refers to cannabis extract.